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A JOURNAL OF NEUROLOGY

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A Journal of Neurology

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MARCH 1960

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VOL. 83, PART 1.

SPONTANEOUS CEREBELLAR HÆMORRHAGE

A STUDY OF 34 CONSECUTIVE CASES TREATED SURGICALLY

BY

WYLIE McKISSOCK, ALAN RICHARDSON AND LAWRENCE WALSH

(*From the Neurosurgical Department, St. George's Hospital, London, S.W.*1)

WITH recent advances in radiological and surgical techniques, the interest in all types of cerebrovascular disease has increased, so that major advances have been possible in the surgical management of occlusive vascular disease and of vascular anomalies.

Considerable literature also exists regarding the management of primary intracerebral hæmorrhage, but there is scant mention of the problems of spontaneous hæmorrhage into the cerebellar hemispheres, presumably it is considered a rare lesion.

That this is a misconception has been shown by the work of Kron and Mintz (1927) and by Mitchell and Angrist (1942) who found that hæmorrhage into the cerebellar hemispheres accounts for nearly 10 per cent of all spontaneous intracerebral hæmorrhage, the incidence being strictly in proportion to the weight of brain concerned—the cerebellum representing 10 per cent of the total weight of the brain.

In reviewing our cases of primary intracerebral hæmorrhage over a twelve-year period a total of 308 cases was found, of which 26 involved the cerebellum. Cerebellar hæmorrhage, therefore, comprises nearly 8 per cent of the total, this of course only representing those cases selected for admission to the Neurosurgical Department, and not necessarily representing the true incidence.

We propose to consider 34 cases of spontaneous hæmorrhage into the cerebellum admitted under the care of one of us (W. McK.) either to the National Hospital, Queen Square, or to Atkinson Morley's Hospital from June 1946 to January 1959, these cases comprising the 26 previously mentioned to which have been added 8 cases due to vascular anomalies presenting similar problems.

Ætiology and pathology.—The causes of cerebellar hæmorrhage are

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usually given as angioma, aneurysm, blood dyscrasia, syphilis and infection, whilst hypertension and atheroma have also been held responsible. In these latter cases it has been suggested that hæmorrhage is due to rupture of that branch of the anterior superior cerebellar artery supplying the dentate nucleus (Bailey, 1948; Dow *et al.*, 1958). Alternatively it has been suggested that the hæmorrhage may be venous in origin (Kinnier Wilson, 1955; Courville, 1950), whilst the possibility that some may be hæmorrhagic infarctions has not been overlooked. The situation regarding ætiology is therefore identical with that relating to supratentorial hæmorrhage, in which the cause is demonstrable in many, speculative in some and, in a few cases, completely unknown.

In the 34 cases under review the findings were:

Hypertension (presumed cause) ..	22
Angiomas	6
Aneurysms	2
No cause	4

These findings agree with those of Hyland and Levy (1954) who thought hypertension to be the single commonest cause.

The extent of the lesion varied considerably in individual cases, the left cerebellar hemisphere being more commonly affected than the right and the hæmatoma rarely measuring less than 4 cm. in diameter. The hæmorrhage appeared to start either deep in the hemisphere or in the vermis, being thereafter either confined to the hemisphere, rupturing into the fourth ventricle or to the surface, or extending into the brain-stem. The situation of the lesions in our cases was as follows:

Confined to the hemisphere	18 cases
Rupturing into the fourth ventricle ..	6 cases
Rupturing into the brain-stem	10 cases

In one case the hæmorrhage not only involved the fourth ventricle but also ruptured on to the surface. It also seemed likely that some communication with the fourth ventricle existed in those cases apparently confined to the hemisphere for the presence of blood was demonstrated in the cerebrospinal fluid.

Age and sex incidence presentation.—Most cases occurred in the sixth, seventh and eighth decades, those due to vascular anomalies being in the younger age groups ranging from 15–40 years. The average age incidence was therefore somewhat higher than that reported for similar cases of supratentorial hæmorrhage (David and Hecaen, 1945).

The sex incidence was equal, not showing the female preponderance evident in the large series reported by Mitchell and Angrist.

The lesion therefore most commonly occurred in the more elderly arteriopaths with only occasional cases, occurring in the younger age groups, due to angiomas.

Symptoms and Signs

The onset was sudden in 28 of the 34 cases (82 per cent), there being however no initial loss of consciousness in 18 of these (64 per cent). In 11 patients consciousness was subsequently lost at intervals varying from twelve hours to three days. In 6 patients the onset was ingravescent but in only one was consciousness subsequently lost.

Where consciousness was preserved, or regained, the commonest initial symptoms were occipital headache and vomiting. A small number of patients presented with frank symptoms referable to the posterior fossa such as sudden vertigo, ataxia or clumsiness of a limb. In the remainder onset was characterized by confusion or by the sudden development of a hemiparesis or hemiplegia. We found that at the time of admission to hospital 30 per cent of patients were unconscious, 45 per cent presented with non-localizing symptoms suggestive of a cerebrovascular accident and only in 25 per cent did the symptoms suggest a cerebellar site for the lesions.

The neurological signs presented by these patients were in the main singularly unhelpful. Localizing signs could not be elicited in those patients who were unconscious except that most of them had constricted and non-reactive pupils and periodic respirations. In the conscious patients signs of cerebellar dysfunction were present in less than half. The duration of symptoms lends emphasis to the speed of evolution of the clinical picture.

	24 hrs.	1–3 days	4–7 days	8–11 days	12–15 days	over 21 days
Cases ..	7	6	12	2	3	4
Deaths ..	7	4	11	0	0	3

Presence of Blood in the Subarachnoid Space

In 27 of the 34 cases lumbar puncture was performed, blood being found in 24 and clear fluid in the remaining 3 cases. In 7 no lumbar puncture was performed but from all of these a specimen of ventricular fluid was obtained. Recent hæmorrhage was confirmed in 4 cases, in 1 the fluid was clear and in 2 there was some doubt owing to the length of time since the ictus.

Thus in the 34 cases there was evidence of recent hæmorrhage in 28 (82 per cent), no evidence of hæmorrhage in 4 whilst the findings were dubious in 2.

Clinical Diagnosis

The problems of clinical diagnosis in this condition receive only brief mention in the standard textbooks, presumably as the lesion is considered rare. Kinnier Wilson describes the fulminating type in which consciousness is lost and death ensues rapidly, but also mentions the ingravescent type presenting with meningism and signs referable to the cerebellum

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and brain-stem. Wechsler stresses the transience of the loss of consciousness in many cases, but again emphasizes the prominence of localizing cerebellar signs in the less rapidly progressive cases.

In our experience the problems of diagnosis are considerable largely because of the wide variety in the clinical picture and the multiplicity of possible causes.

INVESTIGATION

The initial investigation of our cases therefore depended on their mode of presentation. In those in whom the presence of subarachnoid hæmorrhage had been established, bilateral carotid arteriography was performed as soon as possible after admission and clinical assessment. This investigation was omitted where the patient's clinical state suggested the presence of a compressing hæmatoma demanding immediate exploratory burr holes and was postponed in those not tolerating consecutive compression of the carotid arteries in the neck.

In 17 patients bilateral carotid angiography was performed and in 16 of them no definite abnormality was reported but in 1 some displacement of the anterior cerebral artery was present suggesting a hemisphere space occupying lesion. In some of those reported as normal a wide sweep of the anterior cerebral arteries suggested early hydrocephalus.

Vertebral angiography was employed after carotid angiography if the clinical picture was suggestive and in those cases in which air studies had shown a posterior fossa lesion associated with subarachnoid bleeding when the necessary delay was considered justifiable. Vertebral angiography was thus performed in 6 cases, in 5 of which no abnormality was reported, and in 1 the presence of spasm rendered the investigation inconclusive. In all 5 with normal vertebral angiograms a large intracerebellar hæmatoma was, in fact, present, in 2 instances being due to an angioma. The number of investigations performed is so small that firm conclusions cannot be drawn, but certainly the presence of a cerebellar hæmatoma cannot be excluded by vertebral angiography.

Patients presenting as cases of acute cerebral compression were treated by exploratory burr holes with three objects in view. Firstly, in a patient admitted in extremis the ventricle could be tapped to assess or reduce the intracranial pressure. Secondly, in view of the clinical diagnostic difficulties, a supratentorial lesion amenable to aspiration might well be present and, thirdly, ventriculography could be resorted to in order to localize the lesion. In the remaining cases presenting with subarachnoid hæmorrhage, ventriculography was employed following negative angiography where persistent neurological signs were present. Ventriculography was also used in those diagnosed as having subacute lesions in the posterior fossa where the nature of the lesion was in doubt.

In 20 cases, therefore, ventriculography was performed, in 19 of which

the lateral ventricles were moderately dilated and normal in the remaining one. In 15 of these a posterior fossa lesion was demonstrated, whereas in 5 the investigation was inconclusive.

Surgical Treatment

Death occurred so rapidly in 6 patients that no investigations or treatment were possible. In the remaining 28 patients the following surgical procedures were performed:

Ventricular tapping	6
Ventriculography only	5
Ventricular drainage only	3
Craniotomy	14

Ventricular tapping was used only in patients in extremis, and ventriculography in the 5 cases mentioned did not establish the diagnosis. Ventricular drainage was instituted in 7 patients, in 4 of whom it was followed by craniotomy but in 3 was the only procedure and was designed to improve the poor clinical state of the patients.

Results of Surgical Treatment

As already stated 6 patients died before surgery was possible, the results in the remaining 28 cases being as follows:

Ventricular tapping only	6 cases	6 deaths
Ventriculography only	5 cases	5 deaths
Ventricular drain only	3 cases	3 deaths
Craniotomy	10 cases	3 deaths
Ventricular drain followed by craniotomy	4 cases	2 deaths

There were thus 9 survivors who were followed up for periods of 1–5 years with an average of two and a half years, during which time no one of them has had a further cerebrovascular episode. The state of the 9 survivors was assessed in the following way: they were considered to be well if able to return to a normal life, minimally disabled if able to resume normal duties but had persistent neurological signs, moderately disabled if only capable of light work or part-time duties and totally disabled if unable to lead a useful existence.

Well	5
Minimally disabled	2
Moderately disabled	2
Totally disabled	0

The 9 survivors out of 34 cases give a mortality rate of 74 per cent, with an operative mortality in the 14 cases subjected to craniotomy of 36 per cent. The influence of the conscious level on mortality at the time of operation will be considered later, but the relevant details in this respect are as follows:

Conscious level at operation	*No. of cases*	*Deaths*
Alert	5	0
Drowsy	7	3
Stuporose	2	2

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Discussion

Cerebellar hæmorrhage, like most cerebrovascular accidents, poses many problems, some of which can now be considered in detail. A review of the clinical data already given may, however, more clearly illuminate some of these difficulties and provide a basis for the diagnosis and management of these cases.

Consideration of the mode of onset shows that it is sudden in over 80 per cent of cases, with initial preservation of consciousness in more than 60 per cent, but that consciousness may be lost very shortly after this in many, whereas in those unconscious at the outset only a few regain consciousness. If the fate of these patients is followed we find that nearly 80 per cent of cases of sudden onset die, whether or not they retain consciousness initially, compared with a 40 per cent death rate in those patients in whom the onset is gradual. These facts taken in conjunction with the duration of symptoms previously mentioned, indicate the rapidity with which these cerebellar hæmorrhages may develop, although in others the hæmatoma may accumulate more slowly, and from this it follows that early diagnosis is of the utmost importance if surgical treatment is to have the best chance of saving the patients.

With this in view, correlation of all the facts produces three major groups of cases as suggested by Michael (1932). The first concerns about 20 per cent of cases in whom the onset is sudden, the subsequent course is rapidly progressive, ending in death within twenty-four to forty-eight hours. In this group cerebellar symptoms usually cannot be elicited, cerebellar signs are absent and the patient presents as one who has suffered a coma-producing cerebrovascular accident with bleeding into the subarachnoid space. In this group the hæmorrhage has usually ruptured into the brain-stem. The second and largest group is composed of patients in whom the onset is sudden with headache, vomiting, vertigo and ataxia, these symptoms subsequently being followed by loss, or impairment, of consciousness. The subsequent neurological findings may give little indication of the site of the lesion, though often the triad of markedly constricted pupils, periodic respiration and fixed deviation of the eyes away from the side of the lesion may be indicative. The latter sign mainly occurs in patients with a contralateral hemiplegia, the eyes then being deviated towards the side of the hemiparesis. The differentiation, however, from hæmorrhage into one cerebral hemisphere is still difficult, and, from a primary brain-stem hæmorrhage, almost impossible. Cases behaving in this way were mostly those in whom the hæmorrhage has ruptured into the fourth ventricle, but a few were due to hæmatomas virtually confined to the hemisphere.

The last group consists of those patients in whom the onset is gradual or episodic, cerebellar symptoms more commonly being related and signs

suggestive of a cerebellar lesion more likely to be elicited. In these the hæmatoma usually appears to be confined to the cerebellar hemisphere although blood may, or may not, be present in the cerebrospinal fluid. Accepting these groups therefore there are at least 20 per cent of patients for whom probably nothing can be done, but the remainder should be considered potentially amenable to surgical cure if managed correctly and expeditiously. In all cases therefore the appropriate investigations, as outlined above, should be undertaken with the minimum of delay, in view of the rapid deterioration which may take place in the patients' condition and the better recovery rates in those "alert" or "drowsy" compared with those in coma at the time of operation. In this context we should consider further those patients in whom survival seemed possible—those of slower evolution where death was thought to be due to the effects of prolonged pressure rather than to massive destruction at the initial ictus. There were 5 patients in this category who were alert for periods ranging from four to twenty-one days, slowly deteriorating during this time and transferred for investigation only when they had become extremely drowsy or, in 3 cases, unconscious. The 2 patients who were drowsy had an established pneumonia on admission and, though they survived the operative procedure, rapidly succumbed to the chest infection in spite of antibiotics and tracheostomy. The other cases were too ill to tolerate any major surgical procedure, dying shortly after admission from large pontine hæmorrhages as a consequence of their cerebellar lesions. In contrast 5 patients were admitted shortly after the incident and were relatively alert at the time of operation, all of whom made good post-operative recoveries.

We must also discuss the defects of surgical management and the problems that arise therein. In 3 cases ventricular drainage was instituted as an initial procedure in patients with signs of high intracranial pressure. In each of these, after some initial improvement, sudden death occurred, in 2 the lesion demonstrated at post-mortem being deemed operable. Our policy now is to establish the diagnosis as soon as possible, and to evacuate the hæmatoma immediately for, with this type of lesion, ventricular drainage is obviously dangerous, possibly from upward herniation of the cerebellum through the tentorium with compression of the brain-stem. The importance of radiological methods of diagnosis must be emphasized and also the need to press this form of investigation to a definite conclusion. As we have mentioned earlier there were 5 cases in which the ventriculogram was inconclusive. In 2 we failed to demonstrate the aqueduct and fourth ventricle and in 2 others the third ventricle was poorly seen and the lesion thought to be in the basal ganglia, these appearances being due to some blood clot in the ventricular system. The ventriculogram in the fifth case was thought to be normal but the views were, perhaps, inadequate. This occurred early in the series and

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we laid little stress on it at the time as the possibility of the diagnosis of cerebellar hæmorrhage had not arisen. We have subsequently insisted on complete visualization of the ventricular system in cases of subarachnoid hæmorrhage with persistent signs, where angiography has shown no causal lesion and where no obvious supratentorial mass is present.

Lastly, we should consider the cause of death in the patients subjected to craniotomy. 2 patients who were drowsy at the time of operation showed some initial improvement but subsequently died from progression of a pre-existing pneumonia whilst the third patient died from a small recurrent post-operative clot associated with massive œdema of the cerebellar hemisphere and consequent tonsillar herniation. Of the 2 patients stuporose at the time of operation 1 was initially improved but died later of pneumonia, the second patient dying during operation. A post-mortem examination on this patient showed that the hæmorrhage had ruptured into the brain-stem. The pneumonia which developed in these patients was treated by antibiotics and early tracheostomy, but it would appear that the infection, and the toxic effects thereof, are well advanced before there is any clinical or radiological evidence of it, the first indication of a pulmonary complication often being a slow deterioration in the patient's conscious level, with increase in the neurological deficit.

With regard to the results in our cases we can find no comparable series in the literature, as they consist mainly of pathological surveys or of isolated cases treated surgically. 1 case was reported by Pilcher (1941) in a man with intermittent symptoms of eleven months duration treated successfully by operation. Le Beau and Feld (1947) reported 2 similar cases in young women and Obrador *et al.* (1952) reported 1 case in a young man presenting as a cerebellar space occupying lesion treated surgically with full recovery, a somewhat similar case due to hypertension being reported by Gross (1955). We have no experience of treating these cases by burr hole aspiration as suggested by Guillame *et al.* (1949) as the hæmatomas have, in our experience, been predominantly solid.

Our survival rate of 9 out of 34 cases is perhaps disappointing, though the operative mortality rate of 36 per cent is not unduly high for so grave a lesion. The fact remains however, as we have seen, that a further 8 or 9 cases might have survived had they been managed more efficiently and the good results attending successful surgery emphasize the need for early diagnosis and surgical treatment. It is probable that only by the evolution of a suitable regime of management and investigation of all cerebrovascular accidents, will the appropriate treatment, whether surgical or medical, be instituted with the minimum of delay and the present death rate from treatable lesions be reduced.

SUMMARY

(1) A series of 34 consecutive cases of spontaneous cerebellar hæmorrhage is presented.

(2) The ætiology and pathology have been briefly considered, and the incidence, mode of presentation and evolution detailed.

(3) The difficulties of clinical diagnosis have been stressed, and the methods of management and investigation explained.

(4) 14 patients were submitted to craniotomy with 9 survivors, an operative mortality of 36 per cent and an overall mortality of 74 per cent. The fate of the survivors has been shown, the good results justifying surgery.

(5) The possible errors of management have been considered, and a plea is made for the urgent investigation and treatment of such patients.

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THE INTRAMUSCULAR NERVE ENDINGS IN MYASTHENIA GRAVIS[1,2]

BY

E. R. BICKERSTAFF AND A. L. WOOLF

(From the Midland Centre for Neurosurgery, Smethwick, Birmingham)

THE development of techniques for better localization of the terminal innervation zone in muscle biopsies (Coërs, 1953*a*, and Coërs and Woolf, 1959), combined with vital staining with methylene-blue and the histochemical demonstration of cholinesterase (Coërs, 1952, 1953*b*; Coërs and Woolf, 1959), has made it possible to demonstrate the intramuscular nerve endings more regularly and far more completely than hitherto. This has enabled us to assemble a considerable amount of information regarding the appearance of the nerve endings in a wide variety of diseases. In this paper we deal with the findings in one disease only—myasthenia gravis—in which the neural tissue has usually been thought to be structurally normal.

In order that the structural changes shown in this study may more readily be appreciated, reference will first be made to the normal pattern.

THE NORMAL TERMINAL INNERVATION PATTERN

Our conceptions of the normal pattern of terminal motor innervation are based largely on the careful studies of Coërs (1955*a* and *b*). Briefly, a terminal motor axon after emergence from the nerve bundle, passes in isolation to the particular muscle fibre it is to innervate, and branching at this stage is minimal or absent. One can express this numerically by the Absolute Terminal Innervation Ratio (A.T.I.R.), viz.

$$\frac{\text{the number of motor end-plates arising from a given number of terminal axons}}{\text{number of terminal axons.}}$$

This was found by Coërs (1955*a* and *b*) in a study of 721 terminal axons in various normal human limb muscles to have a mean value of 1·13 : 1.

[1]This study was aided by a grant from the Muscular Dystrophy Association of America, Inc.

[2]Since this paper was submitted for publication, Coërs and Desmedt have presented their findings in full (*Acta Neurol. et Psychiat. Belgica*, 1959, **59**, 539 to 561). Their results bear a remarkable similarity to ours.

Some of this small deviation from unity is due to the occasional formation of double end-plates on single muscle fibres. Thus the mean Functional Terminal Innervation Ratio (F.T.I.R.), viz.

$$\frac{\text{the number of muscle fibres innervated by a given number of terminal axons}}{\text{number of terminal axons}}$$

was found to be only 1·09 : 1.

In this paper we shall be more concerned with increases in the A.T.I.R. and we may note that Coërs considered that no more than 2·3 per cent of terminal axons should bear double or multiple end-plates.

Coërs, however, was not greatly concerned with the actual form of the end-plate when he made his studies on normal muscles, and for this aspect we have to rely on our own material. Here we have been faced with the great difficulty of obtaining muscle biopsies from normal subjects. Normal limb muscles are rarely exposed except in orthopædic operations and then rarely in such a manner as to enable the terminal innervation zone to be explored, and in those cases in which this has been possible we have, for various technical reasons, failed to obtain satisfactory preparations.

As our studies of myasthenic patients progressed it became apparent that elongation of the end-plate was an important factor, and for this reason we have measured the greatest length of the synaptic area, i.e. the region within which the myoneural synapses are distributed. This, of course, is less a measurement of the true synaptic surface area than an estimate of the length of the muscle fibre in contact with neural structures. In order to be able to compare with controls we have measured also 90 end-plates from 4 cases of mild disease of the lower motor neurone. These measurements are recorded in fig. 1, where it will be seen that only 20 per cent measured more than 25 μ, and as such diseases tend to produce an expansion (though not elongation) of the end-plate it will be appreciated that could we have obtained entirely normal cases for biopsy that figure would have been still lower.

The Present Study

In this paper we shall describe changes in the intramuscular nerve endings observed in biopsies from 7 cases of myasthenia gravis studied by vital staining with methylene-blue and histochemical demonstration of cholinesterase. Case 4 has been reported fully previously (Woolf *et al.*, 1956), and brief reference has been made to Cases 1 and 3 recently (Coërs and Woolf, 1959). The remaining cases have not previously been reported.

The cases fall into two groups—Group I (Cases 1, 2 and 3) in which the biopsy specimens, taken from clinically only slightly affected muscles, showed no inflammatory or degenerative changes in the non-neural

tissues, and Group II (Cases 4–7) in which there were lymphorrhages, increased variation (hypertrophy or atrophy) in size of muscle fibres and, in 2 cases (4 and 7), degenerative changes in other muscle fibres. Though 2 of these cases (6 and 7) showed severe fatigability and at times paralysis of the muscle from which the biopsy was taken, the muscles in the other cases in this group were only slightly affected.

Methods

The biopsies were taken and investigated as detailed in Coërs and Woolf (1959). Electromyographic traces were taken from the exposed muscle in all but Case 3. In all cases hæmatoxylin and eosin staining, vital staining with methylene-blue and histochemical demonstration of cholinesterase were carried out. In some cases Gros-Bielschowsky preparations were made.

Group I

In 2 of the cases in this group the presence of remarkably elongated or multiple end-plates contrasted strikingly with the entirely normal appearance of the non-neural tissues. A congenital case, reported by Coërs and Woolf (1954), in which the elongation of the end-plates was even more striking than in the cases described here, would also fall into this group.

Case 1

Clinical history.—A 32-year-old, married woman, first seen on 3.10.56, had, during her first pregnancy at the age of 30, developed right-sided ptosis, diplopia and dysphagia, together with a weakness of the right hand that was mainly evident in the mornings. For eighteen months these symptoms persisted with many variations until, following a second pregnancy, there was considerable deterioration with bilateral ptosis, variable diplopia, weakness of the palate and larynx, dysphagia and difficulty in getting up from a recumbent position.

Examination revealed weakness and easy fatigability of the eyelids, facial, palatal and pharyngeal muscles and, to a lesser extent, the muscles of the right arm and of the back. These were instantly returned to normal by intravenous injection of tensilon 10 mg., and great improvement was achieved by the regular use of oral prostigmine. Intravenous decamethonium iodide produced symptoms of respiratory embarrassment after 2 mg., but rapid improvement followed intravenous administration of 10 mg. tensilon. Electromyography on the right palmaris longus showed fragmented, short duration and low voltage polyphasic potentials. An intensity-duration curve was normal.

It became increasingly necessary to raise the dosage of prostigmine and thymectomy was carried out by Mr. A. L. d'Abreu. Following this it was possible to maintain the patient on a smaller dose of prostigmine and, when this was changed to pyridostigmine in equivalent dosage, she became symptom free, though fatigability of lids and ocular muscles could still be demonstrated. After eighteen months of excellent health, she developed an acute respiratory infection, suffered a myasthenic crisis and died in a few hours.

Muscle biopsy.—There were no histological abnormalities in the muscle fibres or in the interstitial tissue. Cholinesterase preparations showed a tendency to filamentous subneural apparatuses sometimes giving a wreath-like picture. A piece of muscle taken 15 minutes after intramuscular administration of 2·5 mg. prostigmine showed

only a slight retardation in staining of the end-plates. Vital staining with methylene-blue showed two types of abnormality of the end-plates (figs. 2 and 3), (1) double or even quadruple end-plates arising from a single axon and situated on a single muscle fibre. The terminal expansions of these end-plates were often abnormal, resembling a semicircular disc. In some endings the end-plates were joined together so as to form a single much enlarged and very elaborate terminal arborization, (2) unusually elongated end-plates with terminal expansions of the same type as in (1) arising on either side of a single filament originating from the terminal axon in a T-shaped manner or as a direct continuation. In the latter case it was often difficult to decide where the axon ceased and the end-plate commenced. (Microphotographs from this case are shown in Coërs and Woolf (1959) figs. 208–211.)

Case 2

Clinical history.—A 32-year-old, married woman, first seen on 5.3.58, had developed, four years earlier, left-sided ptosis, which recovered after six months. Two years later, she experienced a fluctuating diplopia for a period of nine months. After three months' interval this returned and became progressively worse in the six months prior to investigation. In the last three months there had been a sense of heaviness of the legs after exertion.

Examination revealed ptosis of the left eyelid and a variable weakness of the external ocular muscles, both these and the palatal and laryngeal muscles showing easy fatigability. The limbs were normal. Tensilon, 10 mg. by intravenous injection produced immediate relief of symptoms. Prostigmine (2·5 mg.) greatly improved, but did not entirely relieve the oculomotor weakness. Oral pyridostigmine in total daily dosage of 400 mg., together with $\frac{1}{2}$ grain ephedrine, t.i.d. relieved her of all but occasional diplopia when tired, and she has been maintained on this dosage.

An intensity-duration curve on the right vastus internus was normal (rheobase 5·9 ma.). Electromyography on this muscle showed a tendency to fragmentation of the motor unit action potentials, although the interference pattern was full.

Muscle biopsy (14.10.58).—The biopsy was taken from the right vastus internus. Electromyographic traces were taken from the exposed muscle before and one minute after intravenous administration of 10 mg. tensilon. No striking abnormalities in the electromyographic traces were observed. Six minutes later 2·5 mg. prostigmine was given intramuscularly, and a further eight minutes later electromyography showed an increased amplitude of the potentials with a very slight tendency to be polyphasic.

Preparations for demonstration of cholinesterase were taken before and eleven minutes after administration of prostigmine. The subneural apparatuses of the end-plates of the first specimen stained with normal intensity, but appeared a little less well defined than normal. In other respects they did not appear abnormal. The specimen taken after prostigmine resembled the earlier specimen except that the intensity of staining was considerably diminished.

Hæmatoxylin and eosin staining showed no abnormality, and in particular there was no evidence of atrophy or hypertrophy of muscle fibres.

Vital staining with methylene-blue (figs. 4 and 5) showed that some of the end-plates consisted of an elaborate terminal arborization of coarsely beaded fibres, while others resembled closely the elongated end-plates in Case 1, showing the same disc-like terminal expansions arising from a long central filament. Occasional end-plates, though drawn out in the line of the muscle fibre, gave an appearance as of shrinkage of the terminal expansions. One terminal axon showed an irregular swelling of its distal portion.

In a third case in this group the changes were far less dramatic and confined to a shrinkage and fusion of the terminal expansions of an

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occasional end-plate. It may be significant that the patient was a boy with only a short history of myasthenia.

Case 3

Clinical history.—A boy, aged 8, first seen on 30.11.56, had a six months' history of variable ptosis and general lethargy, all features being increased after exertion and towards the end of the day.

Examination revealed bilateral ptosis and weakness of facial muscles, while it was easy to demonstrate fatigability of lids and the external recti. There was a very slight fatigability of the limbs.

Prostigmine (2 mg.) by injection produced a definite improvement, but not complete relief of symptoms and ocular muscle fatigability was still demonstrable. Regular oral prostigmine produced a marked and apparently cumulative improvement, which appears to have been maintained.

Muscle biopsy.—The biopsy was taken from the right peroneus brevis. The exposed muscle appeared normal, but it was noted that the subcutaneous tissue appeared a little firmer and less elastic than usual. Hæmatoxylin and eosin preparations appeared normal. Preparations treated to demonstrate cholinesterasic activity showed the subneural apparatuses of many normal looking end-plates, but there were also occasional apparatuses in which the cups appeared to have fused together. Vital staining showed that these changes reflected the state of the neural part of the end-plates since, although the terminal innervation pattern and the great majority of the end plates were entirely normal, an occasional end-plate appeared as though the terminal expansions had shrunk and fused together. This appearance is seen in cases of myositis in areas remote from inflammatory exudates, and in these cases was attributed by us to œdema (Coërs and Woolf, 1959). (Microphotographs from this case appear in Coërs and Woolf (1959) figs. 8, 219 and 220.)

Group II

In these cases the elongation of the end-plates was less easily recognized than in the cases where the biopsy specimens were free from changes in the non-neural tissues. This was because of an accompanying disorganization of the terminal innervation pattern resulting from a remarkable degree of sprouting of the terminal axons after their emergence from the nerve bundle.

Case 4

Clinical history.—A married woman, aged 40, when first seen in October 1954, had noticed weakness of the legs after cycling at the age of 36, followed in the next four years by a progressively severe weakness of the legs after exercise, difficulty in getting out of bed or out of the bath, and in raising her arms above her head. All these features varied greatly, and on some days she thought she was quite normal.

Examination revealed a gross defect of upward and lateral ocular movement, weakness of the facial muscles and of the larynx; weakness of the shoulder girdle muscles and of the left thigh; and inability to sit up without assistance. All these features varied strikingly throughout examination.

Prostigmine (2·5 mg.) by injection produced dramatic return to normality of all muscles affected, and on an oral dosage of 120 mg. prostigmine per day she has remained almost completely symptom free.

This case was reported in detail in 1956 (Woolf *et al.*, 1956). We will only refer here to the remarkable degree of proliferation of the subterminal nerve fibres which

gave rise to many ramifying, beaded sprouts, often ending in diminutive or bizarre terminal expansions. Endings more definitely recognizable as end-plates were often elongated and the synaptic area of any given muscle fibre tended to be further increased by the formation of several end-plates upon it. These end-plates might be derived from different nerve fibres or from a network of branching fibres. Cholinesterase preparations showed some normal subneural apparatuses, but also some composed of very small units spread over a larger area than normal. Bielschowsky preparations showed the subterminal nerve fibres to be a little more delicate, tortuous, and spread out than normal. Orthodox staining with hæmatoxylin and eosin showed lymphorrhages, basophilic staining and atrophy and hypertrophy of muscle fibres. Since publication of the original report we have been able to demonstrate in Bielschowsky preparations degenerative swelling of axons within a nerve bundle in the vicinity of a lymphorrhage (Coërs and Woolf, 1959, Case 6, p. 103). Nerve fibres in another bundle remote from the cellular infiltrations were normal.

Case 5

Clinical history.—A 19-year-old girl was admitted to hospital on 8.1.58, complaining of weakness of the voice developing towards the end of each sentence for the past month, with a previous similar episode six months earlier, lasting one week. On the present occasion she had also developed great difficulty in chewing hard foods and fluids tended to regurgitate through the nose. For two weeks her back muscles had become weak.

Examination revealed marked weakness and easy fatigability of eye, facial and jaw muscles and almost paralysis of palatal and pharyngeal muscles. The back muscles were weak.

Test doses of prostigmine (2·5 mg.) and tensilon (10 mg. intravenously) gave dramatic improvement in all muscle groups.

An intensity-duration curve on the left palmaris longus showed an early take-off, suggestive of partial denervation. She tolerated 2·5 mg. decamethonium iodide intravenously with only slight discomfort—heaviness of eyes and legs—and only a 14 per cent diminution in the height of the potential recorded by surface electrodes over the hypothenar eminence, with supramaximal stimulation of the ulnar nerve at the wrist. These symptoms were promptly reversed and the potential increased to normal amplitude by 10 mg. intravenously of tensilon. Electromyography showed a full interference pattern on maximal effort, but on slight effort, long duration and short duration, polyphasic potentials were detected.

On a maintenance dosage of 540 mg. pyridostigmine per day with additional ephedrine, she has been able to maintain steady employment, but her palate moves very little.

Muscle biopsy (14.1.58).—The muscle biopsy was taken from the right palmaris longus. Hæmatoxylin and eosin staining in paraffin sections revealed groups of atrophic muscle fibres, the lesser affected of which showed the more marked proliferation of sarcolemmal nuclei, while in frozen sections a single pin-head-sized focal accumulation of lymphocytes was observed. Cholinesterase preparations, incubated at pH 4·4, showed—even at six hours—faintly staining subneural apparatuses, rather poorly outlined. This pale staining was probably due to the prostigmine she had been given the previous night. Further sections were incubated at pH 5. This not only confirmed that the end-plates were rather more amorphous than usual, but showed numerous minute (up to 3 μ diameter) foci of cholinesterasic activity in an area up to 300 μ away from the end-plate (figs. 6 and 7). The explanation of these deposits became clear on examining preparations stained vitally with methylene-blue. They represented the point of contact of numerous minute,

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and probably in many instances ultramicroscopic, terminal expansions with the muscle fibre. The expansions were borne by fine ultraterminal (fig. 8) or collateral sprouts (fig. 9), arising from the end-plate or terminal part of the axon respectively. Both these structures tended to be abnormal. The end-plates were frequently unduly elongated or over elaborate (fig. 10) and sometimes poorly outlined, consisting of an irregularly shaped mass of axoplasm. The subterminal nerve fibres also bore unusual irregularly shaped swellings towards the end of their course (fig. 8). Even the nerve bundles showed a disorganized arrangement of their nerve fibres, some of the latter being unduly broad and tortuous and others fine and frequently branching. Bielschowsky preparations showed less strikingly the same features, i.e. leashes of fine nerve fibres, together with irregularly swollen axons (fig. 11). In one area in the immediate proximity of the lymphocytic nodule mentioned above, a more striking proliferation of nerve fibres had led to a tangled network (neurocladism) around single, apparently degenerating muscle fibres (fig. 12). The appearances recalled the arrangement of motor nerve fibres in the juxta-equatorial zone of the intrafusal muscle fibres of the muscle spindle. The sprouting increased in degree as the nodule was approached.

Case 6

Clinical history.—A 60-year-old man was first seen in November 1955, having a seven-year history of progressively more severe, but variable, weakness of the legs followed by weakness of the arms, bilateral ptosis and diplopia. For twelve months he had been practically bedridden and could only remain standing with assistance.

Examination revealed bilateral ptosis, no ocular movement, gross weakness of peripheral muscles of both arms, gross weakness of back muscles, and severe weakness of the proximal muscles of both legs. All were fatigued by the slightest movement.

An injection of prostigmine (2·5 mg.) produced dramatic improvement in the back and leg muscles, considerable improvement in the forearm muscles, but little change in the hands. Slight ocular movement became possible in all directions and the ptosis improved. After maintenance on oral prostigmine for three years he was admitted to hospital in order to supervise the change-over to pyridostigmine.

An intensity-duration curve on the right flexor carpi radialis showed marked evidence of partial denervation. The curve from the right vastus internus was normal. Electromyography on the right deltoid showed a tendency for the motor unit action potentials to be fragmented. The right palmaris longus yielded very few action potentials on volition, those present being of low voltage but normal duration. The interference pattern obtained from the right vastus internus was at first normal, but after 10 sec. of voluntary contraction the potentials decreased markedly in amplitude, although there was no noticeable difference in frequency.

Muscle biopsy (11.11.58).—The patient was given no anti-cholinesterase drug on the day of biopsy. The muscle biopsies were taken from the *right flexor carpi radialis* and the *right vastus internus*.

The right *flexor carpi radialis* appeared paler than normal and its lateral part appeared distinctly duller than the medial. The motor point was poorly defined.

Electromyography on the exposed muscle yielded no action potentials on attempted volition.

Hæmatoxylin and eosin staining on a fasciculus taken from the lateral portion of the muscle showed very hypertrophic muscle fibres, separated by small groups of extremely slender fibres (fig. 13). These slender fibres showed a tendency for their sarcolemmal nuclei to coalesce into elongated masses of nuclear material which tended to occupy the entire breadth of the muscle fibre (fig. 14). Transverse sections of this portion of the muscle showed large focal collections of lymphocytes, in the

midst of which muscle fibres, apparently unaffected, could be seen, though it seemed probable that some muscle fibres had completely disappeared, their place being taken by the lymphocytes (fig. 15). A fasciculus from the medial part of the muscle, whose surface had had a more normal naked-eye appearance, also appeared more normal histologically, though there was a tendency for the sarcolemmal nuclei to form groups.

Cholinesterase preparations showed the subneural apparatuses of the end-plates to be spread over a wider area than normal. Some muscle fibres showed a series of single cups at widely separated intervals along their course. These tended to be situated on slender muscle fibres, other fibres showed a normal, or only slightly reduced number of units more widely spread out than normal, suggesting hypertrophy of the muscle fibres. These muscle fibres did indeed tend to be broader than usual.

Vital staining with methylene-blue showed a marked alteration in the distribution of the terminal motor innervation. Small leashes of nerve fibres ran parallel with the muscle fibres becoming increasingly delicate and dividing rapidly into even finer branches, which terminated in diminutive terminal expansions (fig. 16A). These terminal arborizations could be easily recognized because of the presence in their vicinity of histiocyte-like cells whose processes were clearly demonstrated by vital staining. These changes in the terminal axons did not appear to be very strikingly related to the lymphorrhages referred to above. The original end-plates in this case were difficult to identify, the most common type of ending being the diminutive terminal expansions borne by the delicate short collateral branches of the axons wandering parallel with the muscle fibres. Occasionally a more elaborate end-plate was seen and this then showed a tendency to elongation (fig. 16B).

The biopsy from the right *vastus internus* showed muscle with a normal naked-eye appearance except possibly for some excess of fat. Specimens were taken for cholinesterase staining before and after administration of prostigmine. The electromyography traces which, before the administration of prostigmine had only shown very low voltage long duration potentials, ten minutes after the administration of prostigmine showed a normal electromyographic trace, though with a tendency for the action potentials to fall in amplitude after ten seconds of volitional activity.

Hæmatoxylin and eosin stained preparations showed striking lymphorrhages and groups of atrophic and hypertrophic muscle fibres, as was seen in the lateral part of the specimen from the *flexor carpi radialis*, but not to such a severe degree.

Cholinesterase staining in both the specimens showed no end-plates before three hours' incubation and even then there was only very diffuse staining. A piece of muscle was taken for vital staining with methylene-blue, but unfortunately did not appear to contain the terminal innervation.

Case 7

Clinical history.—We are indebted to Dr. J. MacDonald Holmes for permission to include this case.

A 46-year-old, married woman was admitted to the Midland Centre for Neurosurgery on 18.5.58, having had a three-year history of diplopia, slurring of speech, difficulty with swallowing and general tiredness, always increased by exercise, though often worse first thing in the morning. Two months after onset a thymectomy was carried out and a small thymoma removed. There was no improvement.

Examination revealed marked weakness of the lids, ocular muscles, palatal, pharyngeal and laryngeal muscles, all of which were easily fatigued, but greatly improved by injection of tensilon, and improved by oral dosage of pyridostigmine, amounting to 720 mg. per day. To this was added a daily dosage of 50 units ACTH, but only partial relief of symptoms was obtained by any of these measures.

Decamethonium resistance test.—A preliminary surface electromyogram was taken

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from the right hypothenar eminence while the ulnar nerve at the wrist was stimulated percutaneously at 10 per sec. with supra-maximal stimuli of 0·1 millisec. duration. 1 mg. decamethonium was injected intravenously. After about 1 minute the patient became unable to speak or to swallow. She was given 1 c.c. (10 mg.) tensilon I.V.N.B. This did not appear to affect her swallowing or speech. An electromyogram before the administration of tensilon showed an increase in the size of the potential and her grip was very strong. She became able to say a word or two after a few minutes, but her inability to swallow lasted much longer and it was still necessary to suck out saliva from the pharynx at 15 minutes. At 15 minutes, atropine 1/50 gr. was given intravenously and at 20 minutes the patient could swallow a little, but not her tablets. 2·5 mg. prostigmine was injected intravenously with marked improvement and a few minutes later she swallowed her mestinon tablets, and henceforth gradually recovered.

Electromyography on the right deltoid showed marked fragmentation of the motor unit action potentials, though this was not quite as severe as is commonly encountered in muscular dystrophies.

Muscle biopsy (27.5.58).—The biopsy was taken from the right deltoid.

The exposed muscle was normal in appearance except that there were bands of fatty tissue between groups of fasciculi.

The patient, who had been having 180 mg. of mestinon four times daily, was given her last dose at 10.0 p.m. the night previous to muscle biopsy, but was given 90 mg. mestinon at 7.30 a.m. on the morning of the biopsy, which was performed at 9.30 a.m. At this time the patient was very weak with severe ptosis, so that she could barely see out of her eyes, and was unable to sit up.

Electromyography yielded a trace from some fasciculi similar to that obtained previously; these fasciculi were vitally stained with methylene-blue. Other fasciculi showed a greatly reduced interference pattern with very low voltage potentials of increased duration (up to 10 millisec.). These fasciculi were taken for demonstration of cholinesterase.

10 mg. of tensilon was given intravenously and this produced in both areas a marked increase in the voltage of the motor unit action potentials, but they continued to show fragmentation.

Hæmatoxylin and eosin staining showed most of the specimens to be normal apart from the presence of scattered atrophic muscle fibres, but in one small area the sarcolemmal sheaths contained no muscle fibres but a small number of phagocytes with slightly basophilic cytoplasm (fig. 17). The margin of the sarcolemmal tubes was outlined by crescentic cells with more elongated nuclei, but with a similar cytoplasm to the phagocytic cells mentioned above.

This cytoplasm fluoresced a bright red colour with fluorescent microscopy by the technique of Armstrong (1956) using acridine orange at pH 2·7, thus indicating the presence of ribose-nucleic acid.

Cholinesterase preparations showed only a faint indication of the subneural apparatuses even at three hours' incubation at pH 5. Some sections were left as long as twenty-four hours at pH 5 in the incubation fluid, but the apparatuses remained poorly defined with crystalline deposits.

A specimen taken at ten minutes after administration of 10 mg. of tensilon presented a similar appearance.

Vital staining with methylene-blue secured a full demonstration of the terminal motor innervation, the abnormalities of which were largely confined to the distal part of the terminal axons and the end-plates. The latter showed shrinkage of the terminal expansions so that they lost their normally rounded outline and the filaments of the terminal arborizations were unusually delicate. Those more severely affected showed a fine stippling in the situation where some of the terminal expansions might

have been expected. Some of the other end-plates were unduly elongated (fig. 18). The terminal axons extended in a T-shaped manner into two filaments parallel with the margins of the muscle fibres, their small terminal expansions being situated at intervals along the filaments. Occasional fine beaded axonic sprouts were seen to have arisen near the termination of the subterminal axons and some of these ended in single terminal expansions resembling growth cones.

The nerve fibres within the intramuscular nerve bundles appeared normal, but occasional nerve bundles showed an undue number of branching fibres, as many as four branching fibres being seen within 50 μ of the course of the bundle.

Discussion

In Group I the essential change in the end-plates would appear to be an increase in the length of the synaptic area (fig. 1), i.e. the area over which the myoneural synaptic junctions are distributed. This increase is brought about partly by the elongation of the end-plate and partly (in Case 1) by the formation on single muscle fibres of multiple (double and quadruple) end-plates. Only the former is unique, multiple end-plates being seen in many conditions in which the muscle fibres hypertrophy (spastic limbs, dystrophia myotonica, myotonia congenita) although in the Group I myasthenic cases hypertrophied fibres were not apparently present. In addition to being multiple the end-plates showed (in Cases 1 and 2) bizarre hemispherical terminal expansions arising at intervals along a long central filament. This appearance was even more strikingly shown in the case of congenital myasthenia reported by Coërs and Woolf (1954) and is so different from what is usually encountered in acquired disease that we suggested (Woolf, 1958) it might be an example of a dysplastic disorder. This suggestion later found support in Coërs and Desmedt's (1958) finding of 45 per cent of "elongated" end-plates in one case of myasthenia gravis, and, in 5 out of 6 other less severely affected cases, 3–20 per cent of "pathological" endings.

While the elongation of the end-plates can still be recognized in Group II, it is to a considerable extent obscured by the disorganization of the terminal innervation pattern which results from the striking proliferation of the subterminal nerve fibres. This sprouting of the distal 2–300 μ portion of the terminal axons, together with the delicacy of the sprouts and the bizarre and diminutive nature of the terminal expansions they bear, is encountered in myositis (dermatomyositis) and certain neuropathies (e.g. thyrotoxic, carcinomatous, and myelomatous) and would appear in these conditions to be related to the degeneration of muscle fibres and "inflammatory" exudates. Certainly in some of our cases it was most marked in the vicinity of lymphorrhages. It results in an excess of nerve fibres over muscle fibres with an inevitable tendency to multiple innervation of muscle fibres, thus lowering the Functional Terminal Innervation Ratio. It should be distinguished from the functionally more valuable sprouting, soon after or before the emergence

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of the subterminal nerve fibres from the terminal nerve bundles, which accompanies primary degeneration of the lower motor neurone. This latter type of sprouting results in the reinnervation of denervated muscle fibres—collateral reinnervation—so that the Functional Terminal Innervation Ratio is raised.

Even the "myopathic type" of axonal sprouting seen in Group II cases may, however, be of functional importance, extending still further the synaptic area (already elongated in Group I cases). This extension appeared to reach its most impressive dimensions in Case 5, where cholinesterase preparations showed foci of cholinesterasic activity distributed over a very wide area though still centred on the motor end-plate. However, the significance of these disseminated foci of cholinesterasic activity is not yet clear. They tend to be present where there is a very marked sprouting of the terminal axons provided that these sprouts remain immature. It is tempting to correlate the foci with the diminutive terminal expansions borne by these delicate beaded fibres. We would then be justified in concluding that each focus of cholinesterasic activity represents the response of the muscle fibre to contact with the growing tip of an axonal sprout, and constitutes the post-synaptic portion of a miniature myoneural synapse.

However, in cases such as Case 5, in cases of dystrophia myotonica—in which both the number and the dissemination of the foci may far exceed what we have seen in myasthenia (Coërs and Woolf, 1959)—and in an occasional case of non-myasthenic myositis, the number of terminal axoplasmic expansions seen with vital staining accounts for only a small proportion of the foci. It would seem, therefore, that either the contact which initiates the formation of cholinesterase is made by an ultramicroscopic sprout—and there is evidence that in the nerve trunks, at any rate, ultramicroscopic sprouts may far outnumber those visible with the light microscope (Causey and Hoffman, 1955)—or in these diseases muscle fibres acquire the ability to produce cholinesterase spontaneously. No doubt the electron microscope will help to decide which of these possibilities is correct.

It should be stressed that the cholinesterasic activity does not always appear increased even though the area over which it is found is expanded. Case 7 showed a decrease in cholinesterasic activity, although her anticholinesterasic drugs had been reduced to a level at which great weakness was produced at the time of biopsy. The resistance to these drugs, which had developed in her case would not, therefore, appear to be due to a failure of the latter to inhibit the cholinesterase.

In Case 7 some of the end-plates still appeared drawn out, but the synaptic area was not increased as the terminal arborization appeared to have undergone a secondary shrinkage. The evidence of axonal sprouting was more limited than in the other Group II case and this may be related

to the absence of lymphorrhages, though the focal degenerative changes in the muscle fibres were most marked. We were able to show that there was a great increase in ribose-nucleic acid in this area. The possible role of this substance in the production of axonal sprouting has still to be assessed.

In 3 of our cases (1, 2, and 5) a moderate resistance to decamethonium iodide (C10) was demonstrated in the hypothenar muscles. In all these cases, when weakness developed, it was rapidly reversed by the administration of anticholinesterasic drugs. In a fourth case (Case 7) total paralysis of the bulbar muscles developed after only a small dose. At the same time the distal limb muscles showed normal or possibly increased power. This would suggest that the bulbar muscles were at a more advanced (refractory) stage of the disease than the limb muscles (resistant stage) (Churchill-Davidson and Richardson, 1952*a* and *b*, 1953).

Thus our cases showed the myasthenic abnormality of neuromuscular transmission, but the morphological basis of this abnormality is as yet obscure. It is hoped that studies with the electron microscope—now being undertaken—will throw some light on this aspect.

Some reference must be made to the remarkable axonal sprouting in Case 5 in the vicinity of a lymphorrhage. This had so changed the innervation of one extrafusal muscle fibre as to cause it to resemble that of an intrafusal muscle fibre. This finding was exceptional in our myasthenic cases, while it appears to be more characteristic of dystrophia myotonica. We shall not, therefore, enlarge on the remarks we have previously made (Coërs and Woolf, 1959) regarding the parallelism between both innervation pattern and contractile properties of the extrafusal muscle fibres in the latter disease, and normal intrafusal muscle fibres.

In conclusion, therefore, we have on the one hand what appears to be a primary abnormality in the end-plates possibly dysplastic, but absent in the case with the shortest history. On the other hand, we have changes which tend to obscure the primary abnormality and which are indistinguishable from those encountered in myositic and some myopathic muscles and are probably secondary to "inflammatory" exudates (lymphorrhages) and degeneration of muscle fibres. These changes would not appear to fulfil a primary role in the pathogenesis of the myasthenia, since in most cases of myositis and myopathy in which they are present, myasthenia is absent. However cases of myositic myasthenia have been described (Störtebecker, 1955; Rowland, 1955) and changes in the reaction of patients with carcinomatous myopathy to muscle relaxants have been reported by Croft (1958). There are, in addition, other possible factors to be considered, e.g. the effects upon the end-plate of stretching and shrinkage of the surface membrane of the muscle fibre resulting from the hypertrophy and atrophy observed (in Group II

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cases only). Also to be considered are chemotrophic effects upon the terminal axoplasmic structures of hypothetical abnormal substances circulating in the blood or liberated at the end-plates, while decreased or compensatorily increased activity of the muscle fibres consequent upon neuromuscular block may also have its effect.

However, we do not wish to advance beyond our findings, which, though they have not revealed the primary abnormality responsible for myasthenia, will have to be taken into account in any future studies on the pathogenesis of this fascinating disease.

Summary

Muscle biopsies from 7 cases of myasthenia gravis have been studied by vital staining of the nerve endings with methylene-blue and histochemical demonstration of cholinesterase in the subneural apparatuses of the end-plates. 2 out of the 3 Group I cases, in which classical staining methods showed no abnormality of the non-neural tissues, had many elongated or multiple end-plates. The end-plates also showed these features in Group II cases (cases with histological evidence of inflammation—lymphorrhages—and degeneration, hypertrophy and atrophy of muscle fibres), but were to some extent masked by the remarkable collateral axonic sprouting which was probably related to the interstitial changes in the muscle. The elongation of the end-plates, together with the tendency to multiple endings, increases the length of the synaptic area of the muscle fibre. The elongation seems to be characteristic of myasthenia gravis, but it tends to be absent in some cases especially those with a short history, and the end-plates may have a shrunken appearance. It is not at present possible to correlate these changes with the disorder of neuromuscular transmission.

Acknowledgments and Addendum

We wish to thank Mr. G. Gasser and Mr. J. Evans for their help with photography and histological examination.

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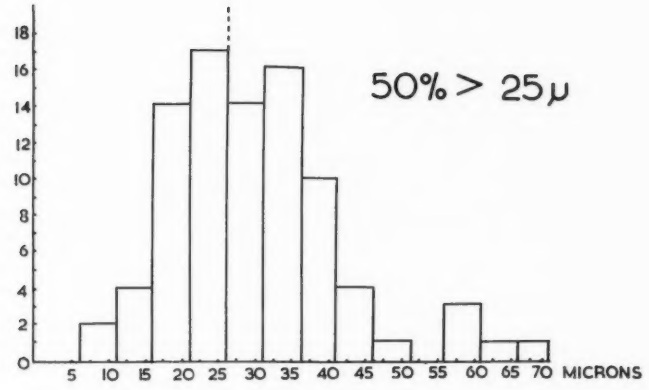
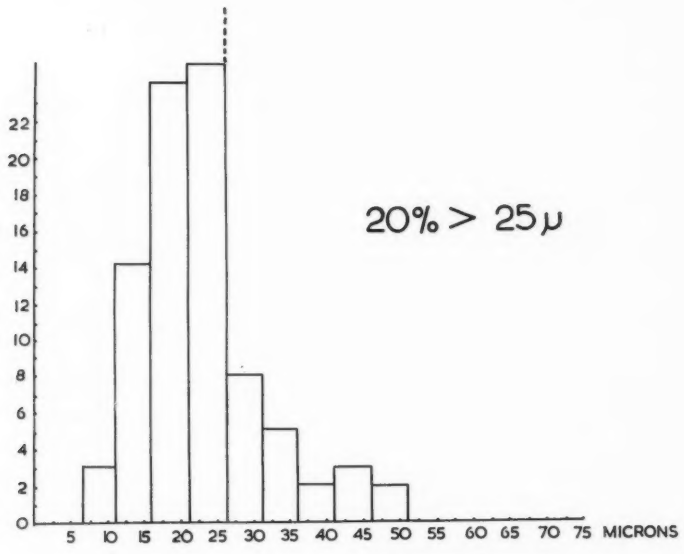
PLATE I



3 CASES OF MYASTHENIA GRAVIS
90 END PLATES



4 CASES OF MILD LOWER MOTOR NEURONE DISEASE
90 END PLATES

LENGTH OF SYNAPTIC AREA

FIG. 1.—A comparison of the length of the synaptic area of the motor end-plates in myasthenia gravis and control cases (mild cases of lower motor neurone disease). N.B. A sufficient number of end-plates from assuredly normal cases was not obtainable (*see text*). Two of the myasthenic cases were from Group I and one from Group II. Ordinate: Number of end-plates in each 5 μ group. Abscissa: Length of synaptic area, i.e. length of area covered by end-plates.

To illustrate article by E. R. Bickerstaff and A. L. Woolf.

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PLATE II

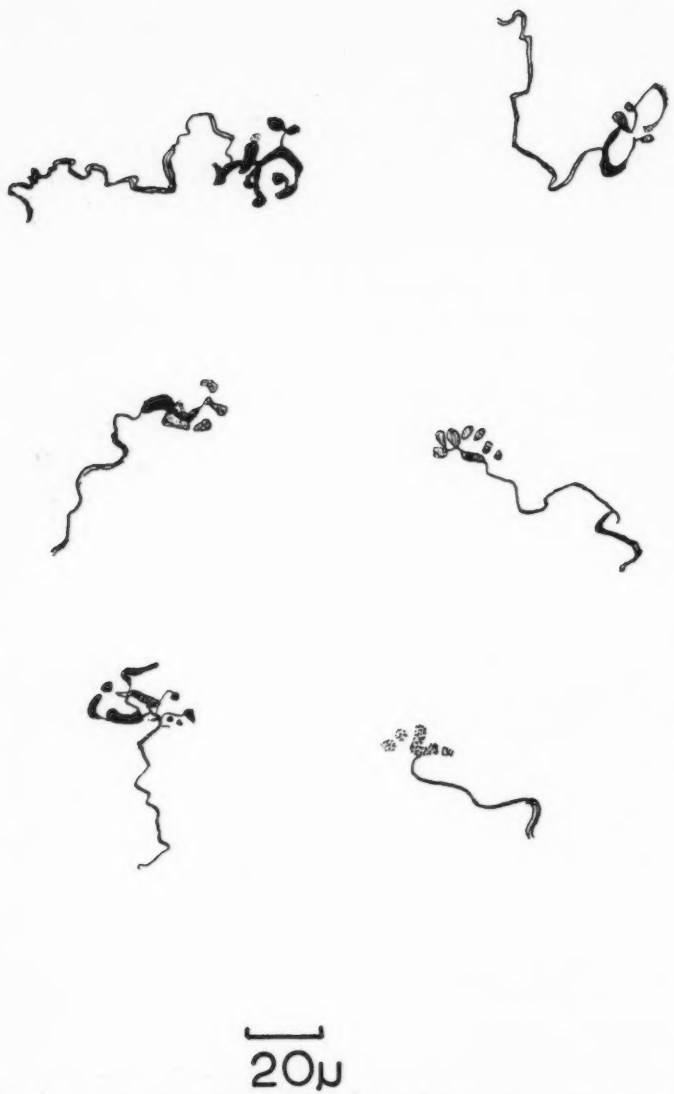

FIG. 2.—Motor end-plates from the muscle of a normal child aged 12. Vital staining with methylene-blue.

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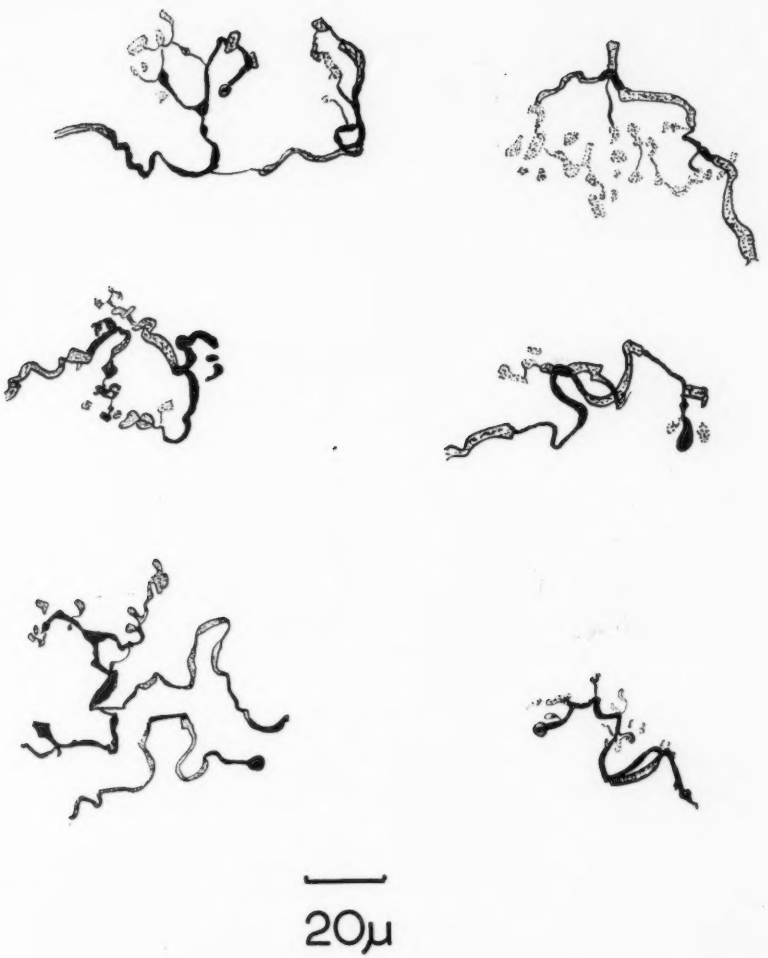

FIG. 3.—Motor end-plates from Case 1, drawn to the same scale as fig. 2. The end-plates are unusually large and tend to be multiple, while the lower two drawings show the elongated type of end-plate. Vital staining with methylene-blue.

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FIG. 4.—Motor end-plates from Case 2, drawn to the same scale as fig. 2. The tendency to elongation is well shown as well as the irregular swelling of the terminal axon and an ultraterminal sprout ending in a club-like ending. Vital staining with methylene-blue.

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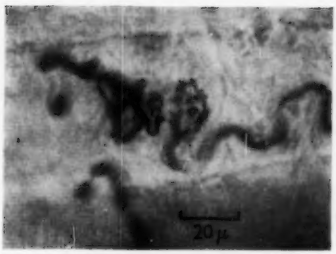

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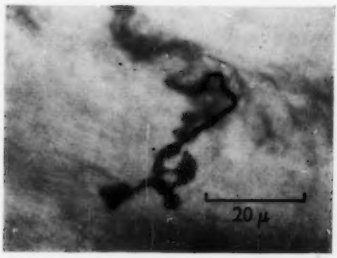

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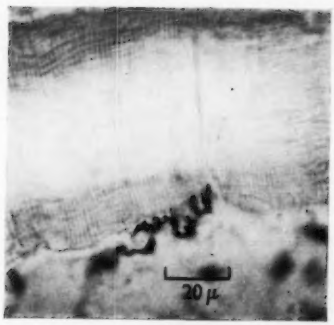

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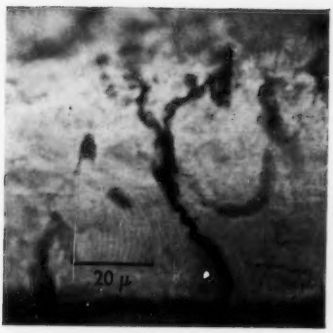

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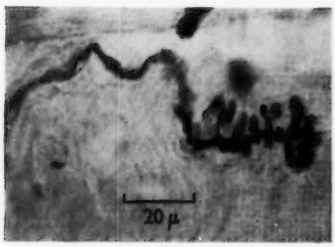

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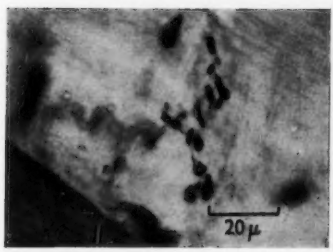

F

FIG. 5 (*Case* 2).—5A and 5C–F, are photographs of the end-plates from which the drawings in fig. 4 were made. 5B shows a drawn out but not greatly enlarged end-plate. Vital staining with methylene-blue.

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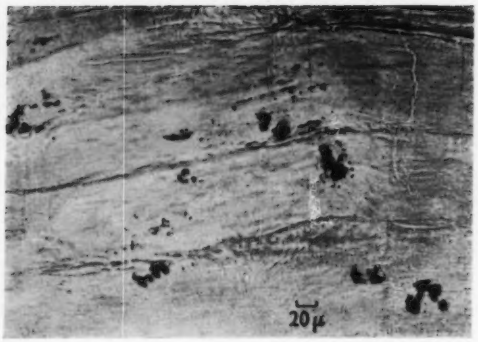

FIG. 6 (*Case* 5).—Cholinesterase preparation to show crude appearance of subneural apparatuses of end-plates and widespread foci of cholinesterasic activity. Modified Koelle's technique.

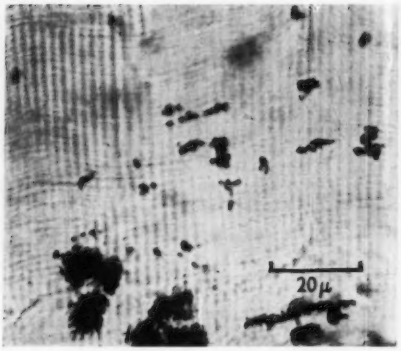

FIG. 7.—As fig. 6, but higher magnification to show form of subneural component of miniature synapses. Modified Koelle's technique.

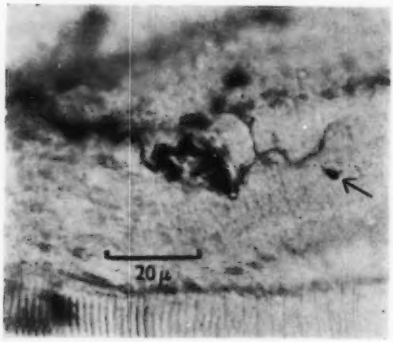

FIG. 8 (*Case* 5).—An ultraterminal sprout bearing a diminutive terminal expansion (arrow) arises from a mass of axoplasm which is probably a degenerated or poorly formed end-plate. Vital staining with methylene-blue.

FIG. 9 (*Case* 5).—Minute collateral sprouts (arrows) arise from an irregularly swollen terminal axon. The sprouts bear diminutive terminal expansions which probably correspond to the foci of cholinesterasic activity seen in figs. 6 and 7. Vital staining with methylene-blue.

To illustrate article by E. R. Bickerstaff and A. L. Woolf.

FIG. 10 (*Case* 5).—Drawing to show extremely elaborate (upper) or elongated (lower two) end-plates. Vital staining with methylene-blue.

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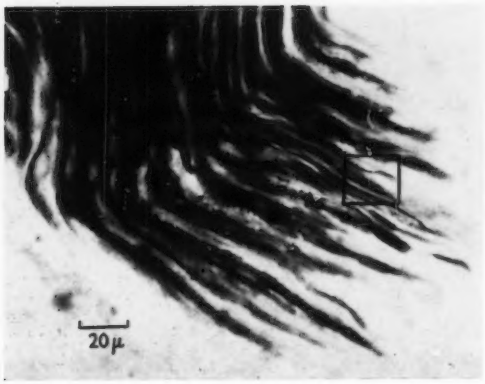

FIG. 11 (*Case* 5).—Intramuscular nerve bundle showing leash of fine nerve fibres (in rectangle) Bielschowsky.

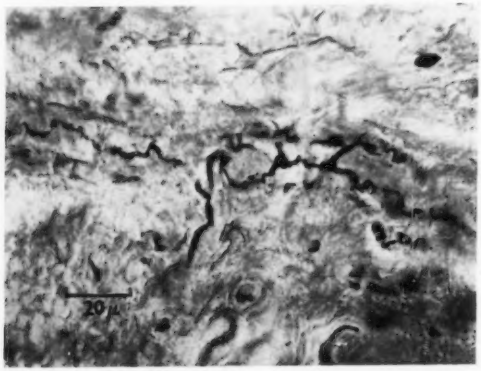

FIG. 12 (*Case* 5).—Conversion of innervation pattern of an extrafusal fibre into that seen in intrafusal muscle fibres in muscle spindles. A lymphorrhage is seen at bottom left. Vital staining with methylene-blue.

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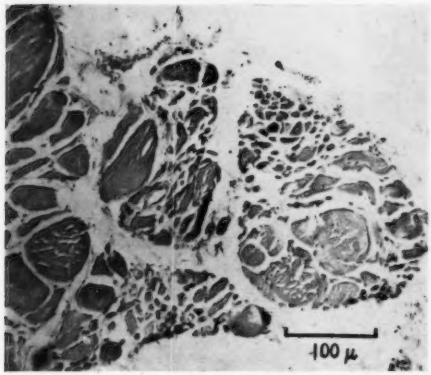

FIG. 13 (*Case* 6).—A single fasciculus contains normal atrophic and hypertrophic muscle fibres. Hæmatoxylin and eosin.

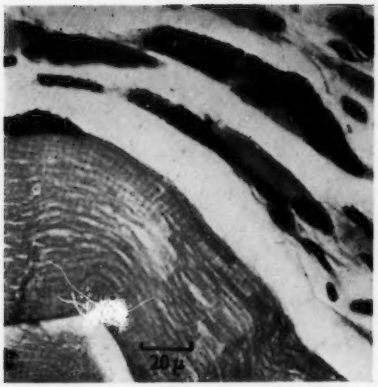

FIG. 14 (*Case* 6).—The sarcolemmal nuclei of some very atrophic muscle fibres have fused and occupy most of the sarcolemmal sheath. Hæmatoxylin and eosin.

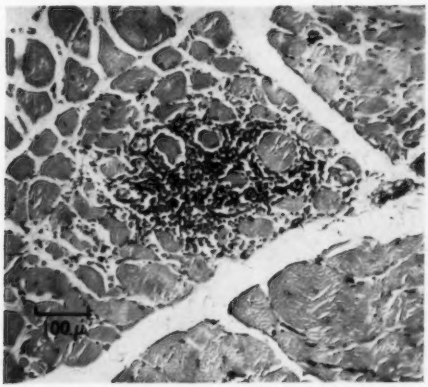

FIG. 15 (*Case* 6).—Apparently normal muscle fibres are seen in the midst of a lymphorrhage. However, some muscle fibres have probably disappeared. Hæmatoxylin and eosin.

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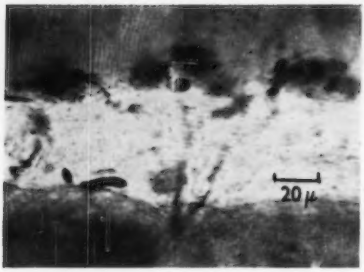


FIG. 16A (*Case* 6).—Three very poorly formed end-plates arise from a single terminal axon and form a greatly lengthened synaptic area on a single muscle fibre. Vital staining with methylene-blue.

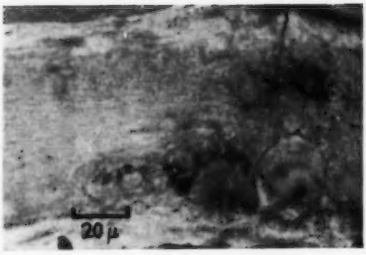


FIG. 16B (*Case* 6).—A very elongated end-plate. Vital staining with methylene-blue.

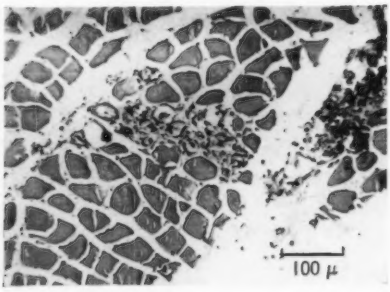
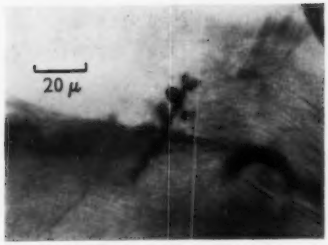


FIG. 17 (*Case* 7).—A well-demarcated area of degeneration of muscle fibres. The empty sarcolemmal tubes contain and are lined by phagocytic cells rich in a substance fluorescing like ribose-nucleic acid. Hæmatoxylin and eosin.

To illustrate article by E. R. Bickerstaff and A. L. Woolf.

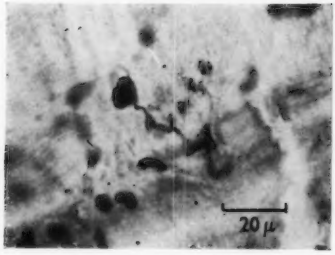
PLATE XI



A

B

C



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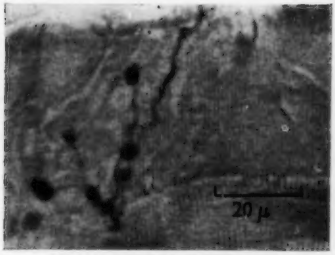

E

FIG. 18 (*Case* 7).—A and B, elongated end-plates. C, shrunken end-plates. D, an end-plate showing swelling of a single terminal expansion. E, a terminal axon bearing several club-like endings. Vital staining with methylene-blue.

To illustrate article by E. R. Bickerstaff and A. L. Woolf.

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THE CHANGES IN THE MOTOR END-PLATE IN MYASTHENIA GRAVIS

BY

VIOLET MACDERMOT

(1) INTRODUCTION

MYASTHENIA GRAVIS has long been recognized as a disorder of neuromuscular transmission. It is, however, only since the introduction of an intravital staining technique suitable for use in muscle biopsy (Coërs, 1952, 1955) that a study of the morphology of intramuscular nerve fibres and motor end-plates has become possible. These structures are not seen with the usual staining methods and until the use of this intravital technique no abnormality in the motor end-plates of muscle in cases of myasthenia gravis was recognized.

Study by early workers of the histology of myasthenic muscle removed post-mortem (Oppenheim, 1887; Shaw, 1890; Jolly, 1895) revealed no significant abnormality. The naming of "lymphorrhages" is ascribed to Buzzard (1905) and the presence of these cells in the muscle has been the main finding in subsequent reports (Keschner and Strauss, 1927; Alajouanine, Hornet, Thurel and André, 1936; Nevin, 1951). "Lymphorrhages" were defined by Greenfield, Shy, Alvord and Berg (1957) as compact aggregations, predominantly of lymphocytes, in sections in which damaged muscle fibres were rare. The presence of other types of leucocytes has also been described (Russell, 1953; Rowland, 1955; Greenfield *et al.*, 1957). A lack of obvious defect of muscle fibres or connective tissue and an absence, in some cases, even of lymphorrhages, were held to be the usual findings by Adams, Denny-Brown and Pearson (1953).

Pathological changes in myasthenic muscle were described by Russell (1953) and three types of abnormality were noted. These types could occur singly or in any combination in a given muscle. In the first type there was necrosis of muscle and inflammatory cellular reaction, in the second progressive muscle fibre atrophy associated with the formation of lymphorrhages, and in the third fibre atrophy only. These changes were not peculiar to myasthenia gravis but there appeared to be a relationship between the histological changes in the muscle and the degree of clinical functional impairment.

Post-mortem examination of the central nervous system in cases of

myasthenia gravis was performed by Oppenheim (1887; 1901) but he and subsequent investigators (Mott and Barrada, 1923; McAlpine, 1929; Westphal and Meyer, 1931; McKendree and Wolf, 1935) failed to find any significant abnormality. The peripheral nervous system was also found to be within normal limits, using routine and silver staining methods (Oppenheim, 1901; Mott and Barrada, 1923; Adams, Denny-Brown and Pearson, 1953).

Abnormal motor end-plates in myasthenic muscle were first demonstrated in one case by Coërs and Woolf (1954) using the methylene-blue intravital staining technique and a modification of Koelle's histochemical method for cholinesterase (Koelle and Friedenwald, 1949). This case and three others (Sandifer, 1955; Woolf, Bagnall Bauwens and Bickerstaff, 1956; Woolf, 1958) were included in a description of nine cases (Coërs and Woolf, 1959). Abnormal end-plates were found in 8 of these cases using the methylene-blue technique. 6 cases, 2 of which had been included in the previous review of 9 cases, were reported by Coërs and Desmedt (1959). In these, two types of end-plate abnormality are described. The first type, to which the name "dystrophic" is given, is seen in other disorders of muscle. The second, or "dysplasic" type is said not to be seen in any condition other than myasthenia. It is stated that these end-plate abnormalities may be present in the absence of any inflammatory or degenerative-changes in the muscle fibres or interstitial tissues (Coërs and Desmedt, 1959; Coërs and Woolf, 1959).

(2) Analysis of the Cases

8 cases of myasthenia gravis are here presented, on whom muscle biopsy has been performed. Abnormalities of the distal nerves and motor end-plates have been found in all cases, using the intravital staining technique (*see* Table III). Routine staining methods were used in addition and in 5 cases little or no abnormality was found; minor abnormalities were present in 2 cases and in 1 case only were there definite changes in the muscle fibres (*see* Table II). The muscle selected for biopsy and electromyography was the deltoid. No clinical fatigability or weakness could be demonstrated in 5 cases and only slight impairment of function in the 3 others. In only 1 of the latter cases did electromyography show a myopathic pattern; in this case and in only 2 others was abnormal fatigability of muscle demonstrated. In all cases a decamethonium and tensilon test was performed by Dr. H. C. Churchill-Davidson and Dr. A. T. Richardson, and in each case the response was characteristic of myasthenia gravis (Churchill-Davidson and Richardson, 1952) (*see* Table I).

The ages of the patients lay between 30 and 60 years. 3 patients were male and 5 were female. The duration of symptoms varied from two months to fifteen years. The muscular fatigability and weakness was mainly confined to the external ocular and facial muscles. Thymectomy

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was performed in 5 cases and the operation was followed by improvement in 4 cases and no change in 1 case. In 2 cases biopsy was performed before thymectomy, in 2 cases after thymectomy and in 1 case both before and after operation. In 1 case the thymus tissue was normal, in 3 hyperplasia was present, and in 1 case there was carcinoma (*see* Table I).

TABLE I

Case	1	2	3	4	5	6	7	8
Sex	M	F	M	F	M	F	F	F
Age	35	44	60	30	43	55	59	45
Duration of symptoms	3 yrs.	2 mths.	6 yrs.	2 mths.	4 yrs.	5 yrs.	6 yrs.	15 yrs
Clinical fatigability of deltoid	0	slight	0	0	slight	0	slight	0
Clinical weakness of deltoid	0	slight	0	0	slight	0	slight	0
E.M.G. fatigability of deltoid	0	+	0	0	0	+	+	0
E.M.G. abnormality pattern	0	0	0	0	0	0	+	0
Decamethonium and tensilon test ..	+	+	+	+	+	+	+	+
Thymectomy	+	—	—	+	+	+	+	—
Histology of thymus ..	Normal	—	—	hyperplasia	hyperplasia	carcinoma	hyperplasia	—

The interest of these cases lies in the fact that while abnormalities of the distal nerve fibres and motor end-plates have been found in each one, and all have given the characteristic response to a decamethonium and tensilon test, yet the muscle selected for biopsy was in most cases both clinically and electromyographically normal or nearly so, and histological abnormality, using routine stains, was slight or absent. A brief account will be given of the techniques used, followed by a summary of the case histories. An analysis of the histological findings will be made, illustrated with diagrams and photographs. Although no firm conclusions can be drawn from such a limited series, an attempt will be made to assess the information obtained.

(3) TECHNIQUES

(*a*) *The technique of muscle biopsy* is described in detail by Coërs and Woolf (1959). In the present series the deltoid has been selected for biopsy in all cases. The end-plate zone of a given fasciculus is localized by electrical stimulation. One strip of muscle is excised for routine staining, in the present cases with hæmatoxylin and eosin, hæmatoxylin and Van Gieson, and a trichrome stain. An adjacent strip is infiltrated with a 0·05 per cent solution of methylene-blue in physiological saline. This strip is then removed and, after processing and fixation, frozen sections of the entire piece of tissue are cut at a thickness of 50–100μ. The nerve fibres and motor end-plates are seen deeply stained against a relatively pale background of muscle fibres. It has been found that the

course of the distal nerve fibres as they travel in three dimensions between the muscle fibres, often forming complex branching arrangements, is extremely difficult to record photographically. Drawings have therefore been made of the appearances seen, recording them as two-dimensional diagrams.

(*b*) *Electromyography* has been carried out as described by Bauwens (1955) selecting for study the deltoid muscle in each case. Using a concentric needle electrode the muscle is explored and the pattern of electrical activity on minimum and on full volition is recorded. The electrical response on nerve stimulation at slow and rapid repetition frequencies is also recorded. Failure of neuromuscular transmission on sustained volition and on nerve stimulation at 10–30/second stimulation frequencies is shown by a gradual decrease in the amplitude of the muscle action potentials. Partial or complete restoration of the potentials to their original amplitude is achieved in cases of myasthenia gravis by giving intravenous tensilon 10–20 mg.

(*c*) *The decamethonium and tensilon test* has been carried out according to the technique described by Churchill-Davidson and Richardson (1952, 1953). 2·5 mg. of decamethonium iodide is given intravenously in divided doses. The ulnar nerve is stimulated percutaneously at a rate of 10/sec. and action potentials derived from the hypothenar muscles are recorded by skin electrodes. In normal subjects widespread paralysis develops together with marked fall of the action potentials. The administration of tensilon 20 mg. intravenously causes an increase of this paralysis. The muscles of patients suffering from myasthenia gravis show a marked tolerance to decamethonium iodide and this tolerance is most marked in those muscles which are clinically normal. The muscles which show the greatest degree of clinical weakness are the first to undergo a failure of neuromuscular transmission. The administration of tensilon 20 mg. causes a rapid restoration of muscle power.

(4) Case Histories

Case 1.—A man aged 35 was admitted complaining of recurrent double vision for three months followed a month later by drooping of the right eyelid and slight weakness of grip. An injection of prostigmine given a month previously had relieved the ptosis and diplopia from which he then suffered and from that time he had taken neostigmine 15 mg. t.d.s. with relief of symptoms.

On examination on this occasion there was no fatigability or weakness of any muscles, even on omission of neostigmine. A decamethonium and tensilon test gave the response characteristic of myasthenia gravis and electromyography showed no abnormality.

Thymectomy was performed and from the day following operation neostigmine was omitted. The thymus tissue was histologically normal.

Biopsy of the left deltoid showed minimal non-specific changes in routine-stained sections. Methylene-blue stained sections showed abnormalities of the distal nerve fibres and motor end-plates.

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Case 2.—A woman aged 44 was admitted complaining of drooping of the left eyelid for two months and double vision for two weeks. In the past she had undergone myomectomy for uterine fibroids five years previously and tonsillectomy one year previously.

On examination there was left ptosis, bilateral impairment of upward gaze, especially on the left, and weakness of abduction of the left eye. The upper limbs were fairly easily fatigued and slightly weak. Tendon reflexes were brisk.

An injection of tensilon 10 mg. produced immediate improvement. A decamethonium and tensilon test gave the response characteristic of myasthenia gravis and electromyography showed abnormal fatigability only.

Biopsy of the left deltoid showed minimal non-specific changes in routine-stained sections. Methylene-blue stained sections showed abnormalities of the distal nerve fibres and motor end-plates.

Case 3.—A man aged 60 was admitted complaining of drooping of the left eyelid for five months and of intermittent diplopia for about six years. In the past he had been treated for pulmonary tuberculosis at the age of 31 by means of artificial pneumothorax but otherwise had been well. He was able to work as a waiter without difficulty.

On examination there was slight left ptosis with bilateral limitation of abduction and fatigability of ocular elevation. No fatigability or weakness could be demonstrated in the limbs. A decamethonium and tensilon test gave the response characteristic of myasthenia gravis and electromyography showed no abnormality. Relief of symptoms followed administration of prostigmine 15 mg. t.d.s.

Biopsy of the left deltoid showed slight non-specific changes in routine-stained sections. Methylene-blue stained sections showed abnormalities of the distal nerve fibres and motor end-plates.

Case 4.—A woman aged 30 was admitted complaining of double vision for two months and of drooping of the left eyelid for five weeks. She had noticed no weakness of the limbs.

On examination there was bilateral ptosis, more marked on the left. Elevation of the eyes was impossible and movements in all other directions were limited and easily fatigued; partial restoration of power occurred following injection of prostigmine. Other muscles were normal. A decamethonium and tensilon test gave the response characteristic of myasthenia gravis and electromyography showed no abnormality.

Thymectomy was performed with no immediate change in her myasthenic state. Her symptoms continued to be partially relieved with prostigmine 15 mg. q.d.s. The thymic tissue showed hyperplasia only.

Biopsy of the left deltoid showed, in routine-stained sections, no abnormality except for a few small perivascular foci of mononuclear cells. Methylene-blue stained sections showed abnormalities of the distal nerve fibres and motor end-plates.

Case 5.—A woman aged 43 was admitted complaining of double vision, drooping eyelids, and weakness of the shoulders and neck for four years. At the onset there had been difficulty in chewing and nocturnal dyspnœa which progressed until a year before admission. At that time she was taking mestinon 65 mg. 22 tablets daily. For four weeks before admission she had reduced the dose to 8 tablets daily and had noticed improvement in her symptoms.

On examination there was slight bilateral ptosis, fatigability of external ocular movements and limitation of elevation and abduction of the right eye. Jaw muscles, facial muscles and sternomastoids were slightly weak. There was slight generalized weakness of the limbs and trunk, most marked in the shoulders. Tendon reflexes

were present. A decamethonium and tensilon test gave the response characteristic of myasthenia gravis and electromyography showed no abnormality.

Thymectomy was performed and slight symptomatic improvement was noticed a month after operation. The thymus tissue showed hyperplasia.

Biopsy of the left deltoid showed no abnormality in the routine-stained sections. Methylene-blue stained sections showed abnormalities of the distal nerve fibres and motor end-plates.

Case 6.—A man aged 55 was admitted for investigation following an episode eighteen months previously when delay in recovery from an anæsthetic had led to the making of the diagnosis of myasthenia gravis. In the past he had noticed two transient episodes of weakness of the hands and legs, five and four years previously. For the past eighteen months he had taken prostigmine 15 mg. q.d.s. and had remained symptom-free.

On examination he showed no abnormal physical signs. After deprivation of prostigmine for three days he showed slight left facial weakness which recovered following an injection of tensilon 10 mg. A decamethonium and tensilon test gave the response characteristic of myasthenia gravis and electromyography showed abnormal fatigability only. X-ray of chest showed an oval opacity in the anterior mediastinum.

Biopsy of the left deltoid showed, in the routine-stained sections, little abnormality of the muscle fibres, but a few small collections of mononuclear cells were present between the fibres. Methylene-blue stained sections showed abnormalities of the distal nerve fibres and motor end-plates.

Thymectomy was performed and histological examination showed carcinoma of the thymus. Three weeks after operation prostigmine was omitted and the patient remained symptom-free until fifteen months later when he was readmitted complaining of double vision.

On examination there was bilateral ptosis and facial weakness, more marked on the right. External ocular movements were fatigable and limited in all directions. There was no fatigability or weakness of his limbs. No radiological evidence was found of a recurrence of the thymoma. His symptoms were partially relieved on prostigmine 15 mg. four-hourly.

A second biopsy taken on this occasion from the right deltoid showed no abnormality in the routine-stained sections. Methylene-blue stained sections showed abnormalities of the distal nerve fibres and motor end-plates similar to those seen in the first biopsy.

Case 7.—A woman aged 59 was admitted for the second time for investigation. On her first admission six years previously she had complained of double vision and generalized weakness for a year. A decamethonium and tensilon test had given the response characteristic of myasthenia gravis. At that time she was almost helpless without prostigmine. Thymectomy was performed and she improved progressively for the following five years. The thymic tissue showed hyperplasia only. The dosage of prostigmine was reduced from 18 to 4 tablets (15 mg.) a day and on this she was able to do her housework.

Examination on the second occasion showed fatigability of the eyelids and of the jaw and neck muscles. There was slight weakness and fatigability of the upper and lower limbs and of the trunk muscles. Electromyography of the deltoid showed a pattern of low amplitude short duration potentials which fatigued rapidly. Partial restoration of the pattern occurred on injection of tensilon 10 mg. A decamethonium and tensilon test gave the response characteristic of myasthenia gravis.

Biopsy of the left deltoid showed in the routine-stained sections abnormalities of

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the muscle fibres and focal collections of interstitial cells Methylene-blue stained sections showed abnormalities of the distal nerves and motor end-plates.

Case 8.—A woman aged 45 was admitted complaining of attacks of double vision and of drooping of the left eyelid for fifteen years, progressive hoarseness and difficulty in swallowing for four years, and loss of voice for four months. Four years previously a decamethonium and tensilon test had given a response characteristic of myasthenia gravis and from that time she had taken prostigmine regularly. On this occasion there was complete aphonia and some dysphagia but she was able to walk well and to do her housework.

On examination opaque nerve fibres were present in the left fundus. The left eye was fixed and movements of the right eye were extremely limited. The masseter and temporal muscles were wasted and weak. The facial muscles were weak. There was no movement of the palate or pharynx and the vocal cords were immobile in a partially abducted position. The sternomastoids were wasted and weak. The tongue was wasted and could not be protruded. There was no significant weakness or fatigability of the upper or lower limbs and the tendon reflexes were present. Deprivation of neostigmine for forty-eight hours caused a marked increase in the ptosis and dysphagia. A decamethonium and tensilon test was again characteristic of myasthenia gravis but the response to tensilon was slight. Electromyography of the deltoid demonstrated abnormal fatigability of the muscle only.

Biopsy of the left deltoid showed no significant abnormality in the routine-stained sections. Methylene-blue stained sections showed abnormalities of the distal nerve fibres and motor end-plates.

(6) Histology

Routine-stained Sections (*see* Table II)

Abnormal variation in muscle fibre calibre is present in 2 cases only. In Case 7 the variation is mainly slight and diffuse, with occasional groups of atrophic fibres (fig. 7). In Case 8 a few small groups of fibres are atrophic (fig. 8). In the remaining cases no abnormality of calibre is seen.

Increase in number and prominence of subsarcolemmal nuclei of slight degree is seen in all except Cases 4 and 5. Centrally placed subsarcolemmal nuclei are seen in Case 7 only.

A few basophilic staining muscle fibres are seen in Case 7 only. Occasional degenerate fibres undergoing phagocytosis are present in Cases 2 and 7 (fig. 2).

Table II.—Routine Stained Sections

Case	1	2	3	4	5	6	7	8
Variation in muscle fibre calibre ..	0	0	0	0	0	0	+	+
Increase in number of sub-sarcolemmal nuclei	+	+	+	0	0	+	+	+
Central emigration of nuclei	0	0	0	0	0	0	+	0
Basophilic staining of muscle	0	0	0	0	0	0	+	0
Degeneration of muscle..	0	+	0	0	0	0	+	0
Increase of interstitial cells	0	0	0	+	+	+	+	0
Increase of fibrous tissue	0	0	0	0	0	0	+	0
Increase of adipose tissue	0	0	0	0	0	0	0	0
Abnormality of intramuscular nerves..	0	0	0	0	0	0	+	0

Increase in interstitial cells occurs in 4 cases. In Cases 4, 5 and 6 very small focal collections of small mononuclear cells are present, sometimes with a perivascular distribution (fig. 5). In Case 7 the collections are larger and in places surround necrotic muscle fibres.

Slight increase in endomysial fibrous tissue is seen in Case 7 in relation to atrophic muscle fibres. No cases show any increase in adipose tissue.

Intramuscular nerve bundles are present in all except Case 8, and all appear to contain an adequate complement of myelinated nerve fibres.

Methylene-blue Stained Sections (*see* Table III)

In all cases many of the distal nerve fibres, after their emergence from the intramuscular nerve bundles, appear markedly abnormal. Along the course of these fibres are seen swellings and irregularities involving both the axons and the myelin sheaths. In all except Case 4, the distal nerve fibres are abnormally tortuous (*see* figs. 10, 11 and 16).

In all except Case 4, fine beaded non-myelinated fibres are seen, usually accompanying the myelinated fibres but sometimes running alone (*see* figs. 12 and 13).

Abnormal branching of the distal nerves is present in all cases. Short branches, giving rise to complex terminal arrangements, are seen in all cases (*see* figs. 11, 12, 14 and 16). Abnormally long branches, often running for considerable distances parallel to the muscle fibres are also seen (*see* figs. 15 and 18).

Motor end-plates show considerable variation in size and shape. Abnormally large and complex end-plates are present in all except Cases 4 and 7 (*see* figs. 12 and 13). Very small end-plates are also seen in all cases (*see* figs. 10–18). Elongated end-plates are seen in all cases, usually in relation to complex branching arrangements where the nerve fibres run parallel to the muscle fibres (*see* figs. 11, 12, 15, 17 and 18). There appear also to be intermediate forms and transitional stages between the various end-plate appearances (*see* figs. 11, 12 and 14).

In many cases it is the end-plates themselves which appear to form the site of origin of the distal nerve branches. In many end-plates the majority of the telodendria appear to degenerate and disappear, with the exception

TABLE III.—METHYLENE-BLUE STAINED SECTIONS

Case	1	2	3	4	5	6	7	8
Abnormal swellings of axons and myelin	+	+	+	+	+	+	+	+
Abnormal tortuosity of nerves	+	+	+	0	+	+	+	+
Abnormal branching of nerves	+	+	+	+	+	+	+	+
Abnormal length of nerves	0	+	0	+	+	+	+	+
Fine beaded fibres	+	+	+	0	+	+	+	+
Abnormally large end-plates	+	+	+	0	+	+	0	+
Abnormally small end-plates	+	+	+	+	+	+	+	+
Abnormally elongated end-plates	+	+	+	+	+	+	+	+
Ultra-terminal fibres	+	+	+	+	+	+	+	+

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of one or two. Ultra-terminal fibres arise as prolongations of these telodendria which extend beyond the end-plate and run often for considerable distances. They may terminate as an end-plate on the same or another muscle fibre, and at this site a similar process may again be seen.

The original end-plate may persist or disappear.

Ultra-terminal fibres, arising from existing end-plates are seen in all cases. In some cases two or more ultra-terminal fibres, running in opposite directions parallel with the muscle fibres, arise from one end-plate. These ultra-terminal fibres may end in elongated end-plates which in turn may give off ultra-terminal branches. The extended end-plate zone so formed may cover a distance of several hundred microns along the length of the muscle fibres involved (*see* figs. 15 and 16).

(7) Discussion

The degree of abnormality of the distal innervation pattern seen in the methylene-blue stained sections in the present series of cases is extremely striking. The normal arrangement whereby the distal nerve supplying each muscle fibre ends in a single motor end-plate can be seen in fig. 9. Structurally the neuromuscular junction consists of the terminal expansions or telodendria of the axon of the distal nerve lying in grooves in the muscle sarcolemma (Couteaux, 1947). The diameter of the end-plate is normally about 32μ with a variation of $\pm 10\mu$ (Coërs, 1955) and in shape it is usually circular or oval.

Of the two types of abnormal motor end-plates in myasthenia gravis described by Coërs and Woolf (1959) and Coërs and Desmedt (1959), the first type is said to resemble those seen in other diseases of muscle and consists of end-plates which are often large and are associated with a profuse ramification of nerve fibres. The second type consists of elongated end-plates without side branches which are possibly specific to one form of myasthenia. The elongated end-plates are stated not to be present in all cases of myasthenia and the suggestion is made that the cases in which they occur form a nosological group.

In the present series the abnormalities noted in the methylene-blue stained sections are the marked changes in the distal nerve fibres involving the axons and myelin sheatns, the presence of fine beaded fibres, the variation in size and shape of the motor end-plates and the unusual branching arrangements of the distal nerves. It is not possible to relate these changes to degeneration or atrophy of the muscle fibres since they occur in cases where no such changes are seen in the routine-stained sections. These distal nerve abnormalities cannot be related to clinical fatigability or weakness of the muscle. There is no relationship to the age of the patients or to the duration of their symptoms. There is no obvious difference between the findings in those patients where

thymectomy has been performed and those in whom there has been no operation. The histology of the thymus appears to be unrelated.

A common feature in all the present cases is the response to the decamethonium and tensilon test, suggesting that in all there is a similar defect of neuromuscular transmission. Zaimis (1952, 1953) has shown that in mammalian muscle decamethonium produces different types of neuromuscular block varying according to the species and to the muscle tested. Whereas in some animals a depolarization block occurs, in others there is a dual mode of response to the drug. This dual response has some of the features of a depolarization block and others of a competitive block. Churchill-Davidson and Richardson (1953) have shown that, whereas the paralysis produced in normal human subjects in response to decamethonium is due to a depolarization block, in myasthenic patients in the clinically weak muscles the initial response is one of depolarization, and this is immediately followed by competitive block. The action of decamethonium at the neuromuscular junction is similar to that of acetylcholine. It is suggested therefore that in myasthenia gravis there is a dual mode of response of the end-plate to acetylcholine, so that an initial depolarization is followed by competitive block. The findings in the present series of cases suggest that this disorder of neuromuscular transmission is associated with neural abnormalities at the end-plate region. These abnormalities are present, not only in those muscles which are clinically fatigable and weak, but also in muscles which are apparently normal both clinically and electromyographically. It is these muscles which show the increased resistance to decamethonium characteristic of muscle in which a dual response occurs.

From these considerations it appears possible that the neural factor in myasthenia gravis is more important than has hitherto been recognized. The neural abnormalities appear to be present before symptoms appear (Case 6 was diagnosed as a result of delay in recovering from anæsthesia). They precede histological changes in the muscle fibres and are not confined to those muscles which are clinically fatigable and weak. The distal nerve fibres are involved as well as the motor end-plates. Changes are present in the axons and the myelin sheaths and there is an unusual pattern of distal branching. The end-plate abnormalities include elongated end-plates and gradations in size and shape between the different types of end-plate.

It is noteworthy that it is particularly from the end-plates themselves that further distal nerve branches arise. Ultra-terminal fibres have been described in animals during the process of reinnervation after the experimental interruption of nerves (Tello, 1907; Gutmann and Young, 1944; Edds, 1950; Hoffman, 1951). In man they have been described in various types of neurogenic disorder when reinnervation of muscle is taking place (Coërs, 1955; Coërs and Woolf, 1959). Their presence in all the present

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cases of myasthenia gravis suggests that the end-plate abnormality is associated with considerable activity at this region which is probably both degenerative and regenerative in nature.

The end-plate abnormalities, in the early stages of the disease, are quite compatible with normal muscle power. Failure of neuromuscular transmission, when it occurs, may remain localized to certain muscles. Degeneration and atrophy of muscle fibres probably occurs when neuromuscular transmission is partially or completely irreversible and these changes are then associated with clinical weakness. At this stage the electromyogram may show a pattern of low voltage short duration potentials. As is well known, changes in the peripheral nervous system and muscle, in response to any abnormal stimulus, tend to be non-specific and lesions at one level in the lower motor neurone are reflected in changes at other levels. It is therefore not possible, on the basis of the present investigation, to be precise about the ætiology of the end-plate defect. However, the present evidence suggests that in myasthenia gravis this defect is a primary neural one and precedes histological changes in the muscle fibres and clinical impairment of muscle function. This neural defect is associated with an abnormal resistance to depolarizing agents, and with appearances suggesting degenerative and regenerative processes at the end-plate region. The appearances in myasthenia gravis are characteristic but there is, at present, insufficient evidence on which to conclude that they are specific.

SUMMARY

(1) The literature concerning the histology of muscle in myasthenia gravis is reviewed.

(2) 8 cases of myasthenia gravis are presented in which muscle biopsy, using the intravital methylene-blue technique in addition to routine stains, was performed.

(3) In nearly all cases the muscle selected was not clinically fatigable or weak and there was no marked histological abnormality of the muscle when stained by routine methods.

(4) In the majority of the cases the electromyographic findings in the muscle selected were normal.

(5) In all cases the response to the decamethonium and tensilon test was characteristic of myasthenia gravis.

(6) In all cases, in the sections stained with methylene-blue, there is considerable abnormality both of the distal nerve fibres and of the motor end-plates.

(7) The presence of abnormal end-plates is noted, an unusual pattern of distal nerve branching is described, and their significance is discussed.

(8) It is emphasized that no definite interpretation of these neural changes can be made on the basis of the present series, but it is suggested that the defect in myasthenia gravis is a primary neural one.

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LEGENDS FOR PLATES

PLATE XII

FIG. 1 (*Case* 1).—Increase in number of subsarcolemmal nuclei. (Hæmatoxylin-eosin × 280.)

FIG. 2 (*Case* 2).—Localized degeneration and phagocytosis of muscle fibres. Polymorphonuclear leucocytes are present. (Hæmatoxylin-eosin × 280.)

FIG. 3 (*Case* 3).—Increase in number of subsarcolemmal nuclei. (Hæmatoxylin-eosin × 280.)

FIG. 4 (*Case* 4).—Normal muscle fibres. (Hæmatoxylin-eosin × 280.)

FIG. 5 (*Case* 5).—Small perivascular focus of lymphocytes. (Hæmatoxylin-eosin × 280.)

FIG. 6 (*Case* 6).—Increase in number of subsarcolemmal nuclei. (Hæmatoxylin-eosin × 280.)

PLATE XIII

FIG. 7 (*Case* 7).—A group of atrophic muscle fibres lying beside fibres of normal calibre and appearance. (Hæmatoxylin-eosin × 280.)

FIG. 8 (*Case* 8).—A group of atrophic muscle fibres lying beside fibres of normal calibre and appearance. (Hæmatoxylin-eosin × 280.)

FIG. 9.—Normal innervation pattern. An intramuscular nerve bundle breaking up into distal nerve fibres each supplying one motor end-plate. (Methylene-blue.)

FIG. 10 (*Case* 7).—Abnormal swellings of the axons and myelin. Very small end-plates. Tortuosity of nerves. (Methylene-blue.)

FIG. 11 (*Case* 8).—Abnormal swellings of the axons and myelin. Tortuosity and distal branching of nerves. End-plates elongated or small showing ultra-terminal branches. (Methylene-blue.)

FIG. 12 (*Case* 6).—Elongated end-plates and ultra-terminal fibres. Abnormally fine fine beaded fibres running alone. (Methylene-blue.)

PLATE XIV

FIG. 13 (*Case* 1).—Abnormally fine beaded fibres accompanying distal nerves, Abnormally large and abnormally small end-plates. (Methylene-blue.)

FIG. 14 (*Case* 5).—Abnormal swellings of axons and myelin. Elongated end-plates and ultra-terminal branches. (Methylene-blue.)

FIG. 15 (*Case* 5) —Abnormal length of distal nerve fibres. The full extent cannot be included in the figure. Distal branches and elongated end-plates. (Methylene-blue.)

FIG. 16 (*Case* 5).—Abnormal ramification of fine tortuous distal nerve fibres which appear to originate from end-plates. (Methylene-blue.)

FIG. 17 (*Case* 5).—Ultra-terminal fibre from an end-plate forming further branches and elongated end-plates. (Methylene-blue.)

FIG. 18 (*Case* 5).—Abnormal length and tortuosity of distal nerves. Elongated end-plates and ultra-terminal branches. (Methylene-blue.)

PLATE XII

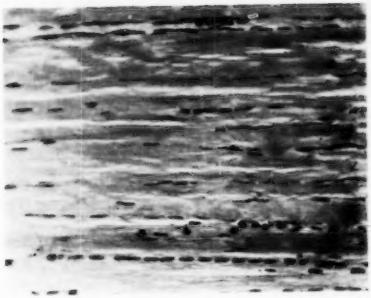

FIG. 1.

FIG. 2.

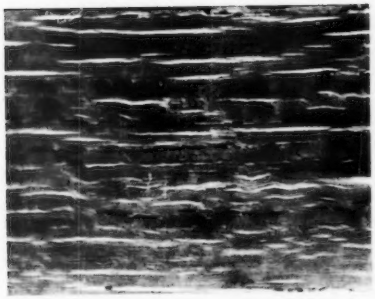

FIG. 3.

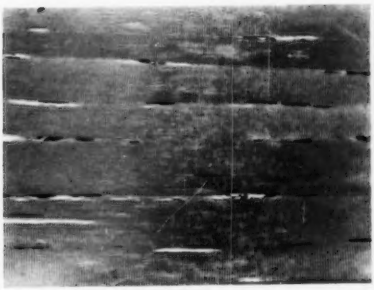

FIG. 4.

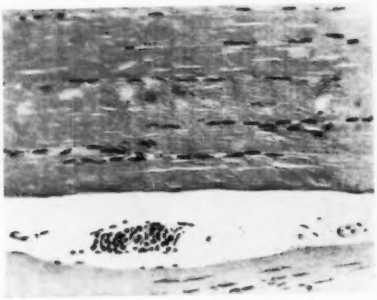

FIG. 5.

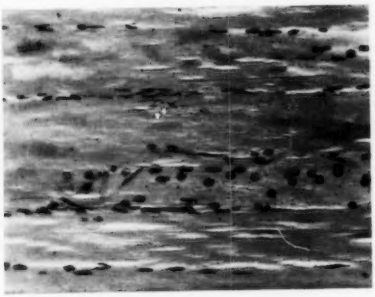

FIG. 6.

To illustrate article by Violet MacDermot.

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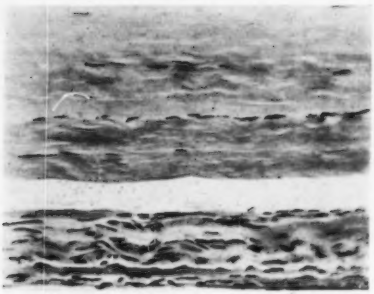

FIG. 7.

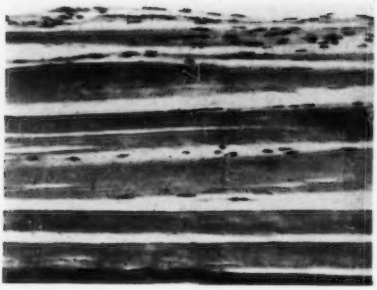

FIG. 8.

FIG. 9.

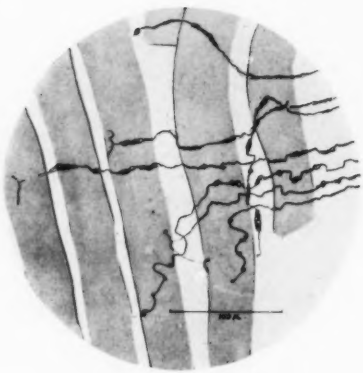

FIG. 10.

FIG. 11.

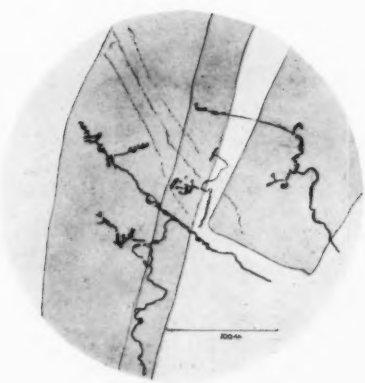

FIG. 12.

To illustrate article by Violet MacDermot.

PLATE XIV

FIG. 13.

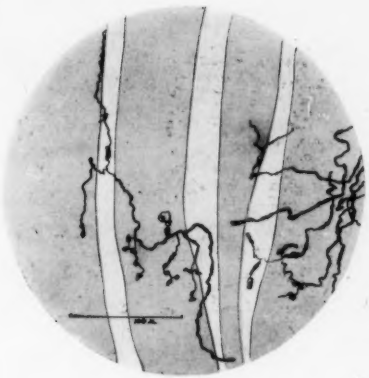

FIG. 14.

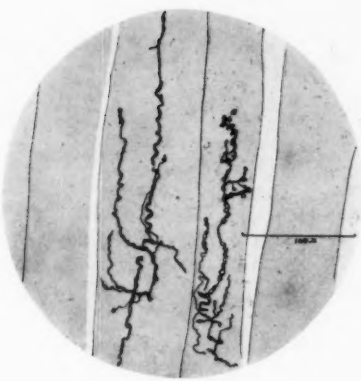

FIG. 15.

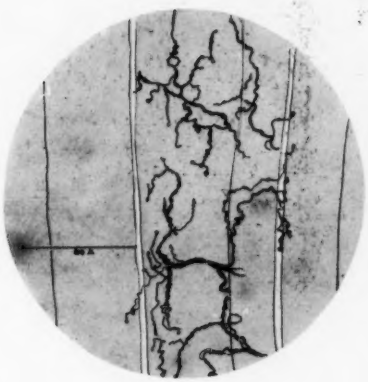

FIG. 16.

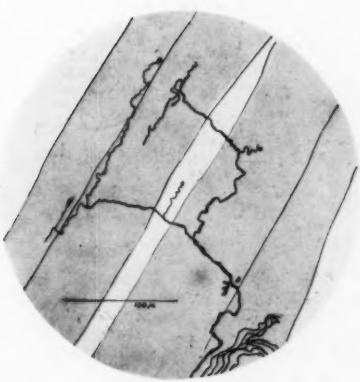

FIG. 17.

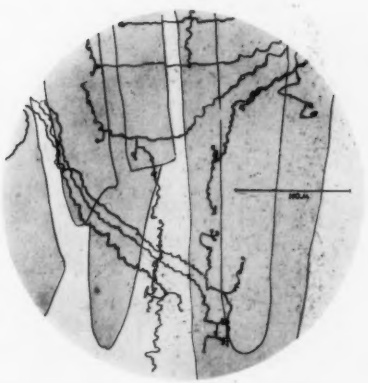

FIG. 18.

To illustrate article by Violet MacDermot.

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A CASE OF CEREBRAL CHROMOBLASTOMYCOSIS (CLADOSPORIOSIS) OCCURRING IN BRITAIN AS A COMPLICATION OF POLYARTERITIS TREATED WITH CORTISONE

BY

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CHROMOBLASTOMYCOSIS is the name by which certain infections caused by naturally pigmented, black or brown fungi—the "dematiaceous fungi"—are usually known. These fungi are not blastomycetes and chromoblastomycosis is therefore really a misnomer, but the term is so commonly used that it is acceptable in the absence of a suitable alternative. There are two main clinical forms of chromoblastomycosis—cutaneous chromoblastomycosis, which is a comparatively common infection in some tropical and subtropical countries, and cerebral chromoblastomycosis, which is a very rare disease, only 15 cases being on record, including the case reported in this paper. Before describing this case a short account of the chromoblastomycoses in general will be given as the subject is not one about which information can easily be got from everyday sources. As far as I know only 3 cases of chromoblastomycosis have been recognized in this country previously—the case of cutaneous infection in an immigrant from Jamaica which was reported by Crow and Riddell (1954), an almost identical unpublished case of mine, also in an immigrant from Jamaica, and a case in which the infection was at first mistaken for rhinosporidiosis because the patient came from Ceylon and the lesion was confined to one side of the nasal septum (Symmers, 1960). All these patients had acquired the infection before leaving their home countries. The patient whose case is recorded in this paper had never been out of England.

Cutaneous chromoblastomycosis.—Cutaneous chromoblastomycosis is a disease of tropical and subtropical lands. Its greatest prevalence is in the Caribbean area, particularly the West Indies; other important endemic centres include parts of Brazil and of South Africa, Madagascar, and Queensland. Cases have been recognized in most countries in the Americas, in various parts of North, East, and West Africa, in India, the East Indies, Japan, and parts of China, and in some eastern parts of the Soviet Union. The disease occurs mainly in those who work barefoot on the land, and in all probability the infection results from contamination of

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minor penetrating wounds by soil or vegetable matter in which the fungus is present as a saprophyte.

The infection ordinarily remains confined to the skin, usually of the leg, and presents as slowly growing, nodular or warty, granulomatous lesions which, over the course of several years, come to cover a considerable part of the limb. Involvement of underlying tissues occurs only exceptionally. Although the distribution of the lesions suggests that the infection spreads along the lymphatics in the skin it is very unusual to find any evidence of extension to the lymph nodes. Dissemination of the infection through the blood stream appears to be extraordinarily rare: Carrión and Koppisch (1933) observed one case in which infection of the skin of one leg was accompanied by what were presumed to be blood-borne metastatic foci of infection in the subcutaneous tissue of the opposite leg and of one arm; the only other record of blood-stream infection complicating cutaneous chromoblastomycosis is a case of cerebral involvement reported by Fukushiro, Kagawa, Nishiyama, and Takahashi (1957)—their case is referred to again later, in the discussion of cerebral chromoblastomycosis.

Mycology.—Several related species of fungi have been isolated from the lesions in cases of cutaneous chromoblastomycosis: the most important are *Phialophora pedrosoi*, *Phialophora verrucosa*, and *Phialophora compactum*, and of these by far the commonest is *Phialophora pedrosoi* (which is also known as *Hormodendrum pedrosoi* and *Fonsecæa pedrosoi*). The mycology of the chromoblastomycoses is complicated and confused, and its detailed consideration is beyond the scope of this paper (*see* Carrión, 1950). One of the more unusual characteristics which distinguish these organisms from other pathogenic fungi is their yellowish brown or greyish colour. They occur in the lesions of cutaneous chromoblastomycosis only in the form of chlamydospores: these are pigmented, rounded bodies, about 10 microns in diameter, with a distinct cell wall, and often divided internally by one or more septa; their size and pigmentation make them easily visible in preparations of infected material, including histological sections, even when unstained. In sections some of them are seen to lie free among the pus cells in the micro-abscesses and suppurating pseudotubercles which are characteristic of the tissue reaction; others are found in the cytoplasm of the multinucleated giant cells which are often numerous in the granulomatous tissue.

When these organisms are growing on artificial culture media, which they do readily, they form abundant mycelium; the different species are recognized by their cultural peculiarities, and particularly by their methods of sporulation. Mycelium does not develop in the lesions of cutaneous chromoblastomycosis, although germinating chlamydospores with one or two short hyphal protrusions are occasionally to be found: this is in remarkable contrast to the lesions of cerebral chromoblastomycosis in which mycelium is characteristically conspicuous.

TABLE I.—CEREBROSPINAL FLUID CHANGES IN PUBLISHED CASES OF CEREBRAL CHROMOBLASTOMYCOSIS

TABLE I.—CEREBROSPINAL FLUID CHANGES IN PUBLISHED CASES OF CEREBRAL CHROMOBLASTOMYCOSIS

Case No.	Authors		Pressure (mm. of c.s.f.)	Protein (mg. per 100 ml.)	Cytology: Total cells per c.mm.	Cytology: Polymorph. per cent	Cytology: Lymphocytes per cent	Cytology: "Monocytes" per cent	Reducing substance (mg. per 100 ml.)	Chloride (as NaCl) (mg. per 100 ml.)	Wassermann reaction	Micro-organisms: Direct exam.	Micro-organisms: Culture	Micro-organisms: Guinea-pig inoculation
3	Garcin *et al.* (1949)	(i)	Ø	150	45·5	20	60	20	Ø	Ø	Negative	Ø	Ø	Ø
		(ii)	N	150	564	64	46 (*sic*)		45	620	Ø	Ø	Sterile	Negative
		(iii)	Ø	85	480	Ø	Ø	Ø	Ø	Ø	Ø	Negative	Ø	Negative
4	Binford *et al.* (1952)		370	70	2	Ø	Ø	Ø	70	700	Negative	Ø	Sterile	Ø
5	King and Collette (1952)		N	60	6	Ø	Ø	Ø	102	Ø	Ø	Ø	Sterile	Ø
6	França *et al.* (1953)	(i)*	Ø	70	501	10	70	20	72	670	Equivocal	Negative	Ø	Ø
		(ii)*	Ø	40	64	0	77	23	65	700	Equivocal	Negative	Sterile	Ø
7	Aufdermaur *et al.* (1954)		130	96	370	78	0	22	19	N	Ø	Ø	Ø	Ø
8	Lucasse *et al.* (1954)		Ø	300	245 (mostly polymorphs)				40	Ø	Ø	Negative	Sterile	Ø
9	Segretain *et al.* (1955); Garcin *et al.* (1957)	(i)	Ø	140	1,350	90	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
		(ii)	Ø	60	490 (mostly lymphocytes)				68	738	Ø	Negative	Sterile	Ø
		(iii)	Ø	40	3,200 (all polymorphs)				70	720	Ø	Ø	Sterile	Ø
12	Fukushiro *et al.* (1957)		200	Ø	10	Ø	Ø	Ø	Ø	Ø	Ø	Negative	Sterile	Ø
14	Manson (1958)	(i)	190	139	26 polymorphs and 9 lymphocytes per c.mm.				65	715	Negative	Negative	Sterile	Ø
		(ii)	160	106	29 polymorphs and 33 lymphocytes per c.mm.				39	691	Ø	Negative	Sterile	Ø
		(iii)	Ø	161	Numerous pus cells				30	618	Ø	†	Sterile	Ø
15	Symmers (1960) (this paper)	(i)	N	105	45	80	20	0	N	N	Negative	Negative	Sterile	Negative
		(ii)	N	140	545 (mostly polymorphs)				Ø	Ø	Ø	Negative	Sterile	Ø

Ø No data available.

N Normal.

* *Case* 6: França and his colleagues (1953) tabulated the results of 11 examinations of cerebrospinal fluid in their paper; the two representative samples included in the table above were obtained by suboccipital tap.

† *Case* 14: Manson (1958) mentioned that acid-fast bacilli resembling *Mycobacterium tuberculosis* were said to have been seen in films made from the third specimen of cerebrospinal fluid in this case. Cultures for tubercle bacilli were negative and no evidence of tuberculous infection was found *post mortem*. He suggested that degenerating mycelial fragments containing pink pigmentary material may have been mistaken for acid-fast organisms.

Cerebral chromoblastomycosis.—A small number of cases of infection of the brain by pigmented fungi has been recorded during the last ten years or so (Table II). The organisms are related to those which cause cutaneous chromoblastomycosis. With one exception there has been no unequivocal evidence of infection outside the central nervous system in these cases. In the exceptional case Fukushiro and his colleagues (1957) isolated *Phialophora pedrosoi* from skin lesions on the patient's face during life and from abscesses in the brain at necropsy. The authors had permission to examine only the brain at necropsy and therefore it was impossible to determine whether there were any lesions elsewhere. The distribution and multiplicity of the cerebral abscesses suggested that they had resulted from dissemination of the infection in the systemic circulation, and it seems therefore to be possible that there may have been chromoblastomycotic lesions in other organs. It is important to note that the phialophora was present mainly in the form of mycelium in the lesions in the brain whereas only the typical chlamydospores were found in the sections of the skin lesions. This observation suggests that the different environmental conditions prevailing in these two tissues, brain and skin, selectively favoured the growth of different forms of the fungus. It is also important that the morphological appearances of the myceliate form of *Phialophora pedrosoi* in the cerebral lesions in this case appear to have been very similar to those of the fungus which was isolated in six of the seven other cases of cerebral chromoblastomycosis in which an organism was grown (Table II): this is the organism which Emmons (Binford, Thompson, Gorham, and Emmons, 1952) named *Cladosporium trichoides*. It is unlikely, indeed, that *Cladosporium trichoides* and the myceliate form of *Phialophora pedrosoi* would be distinguishable either from one another or from related species of fungi merely by their morphology in histological preparations of infected brain tissue: from personal observations I would add that but for their pigmentation it could be difficult to tell these organisms from some species of *Candida* in tissue sections.

One case of cerebral chromoblastomycosis has been reported in which the organism was present only in the form of chlamydospores (Case 6 in Table II) (França, de Britto, and de Almeida, 1953). A very occasional germinating chlamydospore was present but there was no mycelium formation: the fungus in the brain in fact differed in no way from the tissue forms of the fungi in cutaneous chromoblastomycosis, and up to the present the case is therefore without parallel. There were no skin lesions in this case, which occurred in an area where cutaneous chromoblastomycosis is prevalent. Cultures of the organism were not obtained, and its identity with the fungi causing infection of the skin can only be presumed.

Mycology.—The mycelium in histological sections of chromoblastomycotic lesions of the brain shows the characteristic pigmentation very clearly, as a rule, although its colour may be obscured by histological

stains, and by the periodic-acid/Schiff reaction and the like: any myceliate fungus found in such lesions should therefore be re-examined in unstained preparations. The mycelium is rather broad (it is commonly between 2 and 3 microns in diameter); it is pinched in at fairly close intervals (often between 3 and 15 microns apart, and usually constant in length in any given filament), and the filament is interrupted by a transverse septum at each of these points. Branching of the mycelium occurs but is usually sparse; the branches may rise almost perpendicularly but their angle is inconstant. Chlamydospores, which are more heavily pigmented, may be associated with the mycelium and are often split apart as if disrupted by the process of germination; they may also be found singly or in small groups within the multinucleated giant cells of the granulomatous reaction in the tissue forming the wall of the abscesses, while the mycelium, which is much the most abundant and conspicuous form of the fungus in the cerebral lesions, occurs mainly in the exudate forming the contents of the abscesses. Finally, irregularly rounded vesicular structures, 5 to 20 microns in diameter, may be present here and there, interrupting the course of the filaments. While the presence of a fungus with these characteristics in a lesion in the central nervous system would justify a histological diagnosis of chromoblastomycosis the morphological appearances are not alone sufficiently distinctive and constant to permit of these fungi being identified specifically: identification of the species depends on studies of the organism in culture.

Cladosporium trichoides, to which most of the cases of cerebral chromoblastomycosis in the literature have been attributed (Table II), seems beyond doubt to be a distinct species, although closely related to the phialophorae and other fungi which cause cutaneous chromoblastomycosis; some authors in fact have chosen to refer to it as a species of phialophora rather than accept the generic name *Cladosporium*. The cladosporia are a ubiquitous collection of saprophytic moulds; they include among their number only an occasional pathogenic species, such as *Cladosporium wernecki* and *Cladosporium gougeroti*. *Cladosporium wernecki* is the cause of tinea nigra, an epidermal infection met with in the Caribbean region and clinically and pathologically entirely different from cutaneous (dermal) chromoblastomycosis (*see* Conant, Smith, Baker, Callaway, and Martin, 1954). *Cladosporium gougeroti* was generally considered to be a sporotrichum (*Sporotrichum gougeroti*) until Carrión and Silva (1955) showed that it must be considered as a cladosporium. It has been responsible for at least one case of cerebral infection in the absence of any apparent disease elsewhere in the body (Case 7 in Table II) (Aufdermaur, Piller, and Fischer, 1954), thus reproducing the clinicopathological picture associated with *Cladosporium trichoides* infection. Usually, however, *Cladosporium gougeroti* causes a disease of the skin and subcutaneous tissues which clinically has little resemblance to cutaneous

chromoblastomycosis as referred to above: instead, this type of infection is very like sporotrichosis (*Sporotrichum schencki* infection) in its clinical manifestations, although pathologically it is readily distinguished from sporotrichosis by the presence in its lesions of the pigmented chlamydospores which are characteristic of chromoblastomycosis. Only a small number of cases of *Cladosporium gougeroti* infection has been reported (Young and Ulrich, 1953); most of them appear to have been recognized in the southern states of the United States of America, although the case of cerebral infection described by Aufdermaur and his colleagues (1954) occurred in Switzerland.

It is difficult to see how confusion between these different types of cerebral mycosis—infection by the organisms which cause cutaneous chromoblastomycosis, infection by *Cladosporium trichoides*, and infection by *Cladosporium gougeroti*—is to be avoided while there is still so much uncertainty and confusion about the identification and classification of the fungi which cause them.

Pathogenesis.—Nothing is known about the portal of entry of the infection in any of these cases of cerebral chromoblastomycosis, with the exception of the case in which cerebral involvement complicated cutaneous chromoblastomycosis. There is no evidence that the infection reaches the brain from the nose and nasal sinuses as appears usually to be the case with the cerebral mucormycoses; it should be noted that mucosal infection is exceptionally rare in any type of chromoblastomycosis—the case of nasal infection referred to in the introductory paragraph was therefore quite atypical. The pathological findings in fact suggest that the brain becomes infected by organisms carried to it in the systemic circulation: no other route of infection can explain the multiplicity and scattered distribution of the cerebral lesions in most of the cases. There is, however, no information yet about the initial site of infection: the lung is an obvious possibility but pulmonary lesions have not yet been found.

Predisposing causes, such as debilitating diseases, chemotherapy of infections or of malignant disease, or treatment with antibiotics or steroids, which play a part in the ætiology of some cases of other fungal infections, have not been recognized in any of the previously published cases of cerebral chromoblastomycosis. In the case reported in this paper, however, the patient was under treatment with cortisone for polyarteritis when cerebral symptoms began with a stroke which left her hemiplegic; she had had a course of penicillin a few weeks earlier and a second course of penicillin was given during the three weeks between the stroke and her death. The role of penicillin, cortisone, and the underlying polyarteritis in the development of the fungal infection in her case is not clear: the vascular disease, by causing the cerebral infarct which proved vulnerable to the fungus, seems to have determined the site of the

infection, but there is no reason to believe that either it or the treatment predisposed in any other way to the development of the infection or influenced its course.

The geographical distribution of the reported cases of cerebral chromoblastomycosis (Table II), at least half of which occurred in regions with temperate climates, indicates that this type of infection should not be looked upon as exotic: this is in contrast to cutaneous chromoblastomycosis, which appears to be a disease exclusively of hot countries. The case of cerebral chromoblastomycosis reported here occurred in Britain.

Case Report

A woman, aged 22, who had spent all her life on a moorland farm in England, was admitted to hospital because of fever, malaise, and loss of weight. Her health had always been good until a month before, when she began to feel unusually tired after a day's work and to go off her food. Her doctor found that she was running a temperature of up to 101° F. (38·3° C.) in the evenings; when her condition did not improve after a fortnight's course of penicillin (500,000 units daily by intramuscular injection) he sent her into hospital for investigation.

On admission she was pale, listless, and much underweight—she said that she had lost about a stone (6·5 kg.) during the previous month. Temperature 100·8° F. (38·2° C.); pulse 76. There were no other abnormal findings clinically. Red cell count 4,200,000 per c.mm.; hæmoglobin 11·2 grammes per 100 ml.; white cell count 14,000 per c.mm. (80 per cent neutrophiles, 2 per cent eosinophiles, 16 per cent lymphocytes, 2 per cent monocytes). Hargraves test: no L.E. cells found. Urine : protein ++; occasional red cells in the centrifugate. Blood culture in nutrient broth: no growth during four weeks' incubation at 37° C. Widal reaction: no agglutinins to salmonellæ, shigellæ, brucellæ, or leptospiræ. Weil-Felix reaction negative. Paul-Bunnell test negative. Wassermann and Kline tests negative.

A week after admission the patient began to complain of pains in the limbs and vague tingling sensations in the left arm and both feet: the muscles of her shoulders, thighs, and calves were found to be somewhat tender, and there was patchy loss or diminution of skin sensation in some areas and particularly over the feet. Assessment of the neurological findings was difficult as she was too apathetic to co-operate. No abnormality of the reflexes was found. The ocular fundi were normal. Her teeth were free from disease, clinically and radiologically, and radiological examination of her sinuses was normal. Lumbar tap: clear, colourless cerebrospinal fluid under normal pressure; 105 mg. of protein per 100 ml.; excess globulin present; reducing substances and chlorides normal; 45 cells per c.mm. (80 per cent neutrophile polymorphonuclears, 20 per cent lymphocytes); Wassermann reaction negative; no organisms found in films of centrifugate or on culture; a guinea-pig inoculated with cerebrospinal fluid showed no evidence of disease when killed six weeks later.

The diagnosis of polyarteritis was suggested, and a biopsy was done on one gastrocnemius. This showed acute, necrotizing, segmental arteriolitis and periarteriolitis typical of polyarteritis. Up to this time she had had no treatment other than simple symptomatic measures since coming into hospital. A course of cortisone was started: 300 mg. were given daily in divided doses for eight weeks and the daily dose was then reduced to 180 mg. The response to this treatment was remarkably encouraging: her symptoms disappeared, she put on 18 lb. (just over 8 kg.) in weight during eleven weeks, and only a very moderate degree of hypercortisonism developed. She was mentaliy alert and physically active. She became afebrile after the first week on cortisone, leucocytosis disappeared, and her urine was normal except for an

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occasional slight trace of protein. Her blood pressure, which had never been raised, remained normal. The peripheral sensory disturbances gradually passed off, and weekly examination of the nervous system showed no other abnormality.

At the close of the eleventh week of treatment with cortisone the seemingly very satisfactory progress was interrupted when, with no premonitory symptoms, she collapsed in a sudden coma. It was evident that she had developed a left-sided hemiplegia, and this was confirmed when she recovered consciousness. The dose of cortisone was stepped down progressively after the stroke, and the drug was withdrawn completely three days later. Her general condition deteriorated steadily although she remained afebrile. She complained of severe headache and was mentally confused and persistently drowsy. She died three weeks after the stroke. A lumbar tap on the day before her death—the only examination of the cerebrospinal fluid after the stroke occurred—showed a clear, yellow fluid under normal pressure; protein 140 mg. per 100 ml.; cells 545 per c.mm. (almost all neutrophile polymorphonuclears); no organisms were seen in films or isolated on culture (culture was confined to the inoculation of a single blood-agar plate with cerebrospinal-fluid centrifugate: the plate was incubated at 37° C. and was still available six days later when post-mortem histological examination showed the presence of the fungal infection—it was kept for a further four weeks, without any growth occurring).

Necropsy.—A thrombosed aneurysm was present at the origin of a penetrating branch of the right middle cerebral artery; thrombosis extended into the main trunk of this artery and there was softening of the part of the brain supplied by it. The lesion of the brain was assumed to be a straightforward infarct and no cultures were taken; several pieces of tissue were kept for sectioning. It was noted that there was a small number of minute, black granules near the periphery of the lesion. No other abnormality was found in the brain; the ventricles and the meninges appeared to be healthy. There was no disease of the frontal, ethmoid, and sphenoid sinuses or of the middle ears; the maxillary sinuses were not examined. The other organs showed little macroscopical abnormality; there were two small, organizing infarcts in the spleen and one in each kidney.

Histological examination (figs. 1–10, Plates XV–XVIII).—Most of the organs and tissues, including the brain and peripheral nerves, contained healed and healing lesions of polyarteritis, typical of steroid-induced regression of the disease. No acute arteritic lesions were found. A number of the larger visceral arteries showed thrombosed and organizing polyarteritic aneurysms; however, the disease had clearly affected arterioles predominantly. No granulomatous foci and no micro-organisms were found in any of the viscera except the brain. The sections of the cerebral lesion showed extensive necrosis of the brain tissue: basically, the appearances suggested infarction, but the necrotic parts were riddled with discrete or intercommunicating abscesses with many multinucleated giant cells in their walls. A myceliate fungus was present in these abscesses; mycelium was particularly abundant in the exudate immediately lining the wall of the cavities, and less conspicuous in their purulent contents and in the surrounding tissue. Many of the giant cells contained fungal filaments or spore-like structures. The mycelium was dark yellow or brownish in colour and easily seen in unstained sections. In places the feltwork of mycelium formed a collection large enough to be seen by the unaided eye as black granules in the section: these corresponded to the black granules noticed macroscopically at necropsy. The mycelial filaments were constricted at short intervals at the site of transverse septa, and this gave an appearance like a string of oval beads, particularly to the broader filaments. Lateral branching was present moderately frequently; the branches rose at different angles, and sometimes perpendicularly. Rounded structures, about 10 microns in diameter, were also present and appeared to be chlamydospores: they were often more intensely pigmented than the

mycelium; some were split and intimately associated with mycelial fibres, and others were solitary and then usually within the multinucleated giant cells. The appearances of the fungus were identical with those of "*Cladosporium trichoides*" in sections from Cases 8 and 9 in Table II which Professor Vanbreuseghem and Doctor Mariat respectively have kindly lent me for purposes of comparison.

Sections of the cerebral aneurysm showed a picture which was fully consistent with its origin as a polyarteritic lesion, with thrombosis, and with advanced reparative changes in its wall and in the wall of the artery adjacent to it. No fungal elements were found in the aneurysm, in the thrombosed trunk of the middle cerebral artery, or in any vessels in the brain except for those which were within the necrotic lesion itself.

Comment

It is impossible to be sure whether all this patient's symptoms up to the time of the stroke were due wholly to polyarteritis, although the only observation which is not readily attributable to polyarteritis is the unexplained abnormality of the cerebrospinal fluid. The increased protein and cell content without other changes was present when the fluid was examined a week after her admission to hospital (eleven weeks before the stroke); comparable changes were found again on the day before she died, three weeks after the stroke, when their presence was less significant in view of the damage to the brain caused by the vascular disease; these were the only two occasions on which the fluid was examined. Precisely the same type of changes has been reported in the cerebrospinal fluid in other cases of cerebral chromoblastomycosis (Table I), but they are of course by no means peculiar to this disease; on the other hand, such changes in the fluid are not a feature of polyarteritis. The clinical manifestations which led to examination of this patient's cerebrospinal fluid in the first instance were clearly due to the neuropathy associated with the polyarteritic lesions which were demonstrated *post mortem* in the nutrient vessels of the peripheral nerves.

There were no clinical signs to suggest the presence of focal lesions of the central nervous system before the acute development of the hemiplegia, and the eventual pathological findings indicated clearly enough that the latter was the expression of cerebral infarction resulting from vascular occlusion following extension of thrombosis in a healing polyarteritic aneurysm. From the evidence it seems to be very probable that the fungal infection was a secondary phenomenon, developing as a complication of the infarction. It is pertinent to observe that arterial hypertension was present in 2 of the published cases of cerebral chromoblastomycosis (Cases 5 and 13 in Table II) and probably in a third case (Case 7 in Table II), with the possibility that an ischæmic lesion of the brain may have predisposed to the local development of the infection: however, there is no definite evidence in support of this explanation and the pathogenesis of the infection remains obscure. The extent to which the cerebral lesion in the case described here was colonized by the fungus, while very striking, is probably not more than could have resulted in the course of the three

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weeks between the occurrence of the stroke and death. *Cladosporium trichoides* and other organisms which cause chromoblastomycosis are capable of quite rapid growth and could doubtless colonize suitable tissue as speedily and extensively as, for example, *Aspergillus fumigatus* can colonize infarcts in the lungs.

This patient had always lived in England and her case is therefore the first recorded instance of chromoblastomycosis acquired in the British Isles. It is therefore particularly unfortunate that cultures were not obtained. One can only presume that the fact that most of the published cases of cerebral chromoblastomycosis have been due to a species of fungus distinct from those which cause cutaneous chromoblastomycosis makes it likely that the organism in the case under discussion was the same one that had been isolated from these other cases, or a species very closely related to it.

It is probably significant that the patient lived on a farm, for the chromoblastomycoses occur predominantly in countryfolk. The organisms almost certainly have their natural habitat in soil and vegetable matter which they colonize as saprophytes, and it is for this reason that people who live and work on the land are exposed to a greater hazard of infection than is the case with town-dwellers. As nothing seems to be known about the extent to which the dematiaceous fungi which cause the chromoblastomycoses occur in soil, or elsewhere, in this country, speculation on the source of this patient's infection and on the method and site by which the organism entered the body has little point.

The known liability of steroid therapy and of antibiotics to predispose to certain fungal infections, and particularly to blood-stream dissemination of aspergillosis, moniliasis, and the mucormycoses (Zimmerman, 1955), raised the possibility that the development of a cerebral mycosis in this patient's case may have been encouraged by treatment with cortisone and penicillin. The possible significance of this treatment will remain debatable until more is known about the ætiology and the pathogenesis of this type of infection. It is relevant to note that various antibiotics, including penicillin, have been used in the course of attempts to find an effective method of treating cutaneous chromoblastomycosis: there have been no reports that any of them have ever enhanced the pathogenic effect of the organisms or led to dissemination of the infection. Cortisone and other steroids do not seem to have been used in cases of chromoblastomycosis, and nothing is known of their possible effects on the course of the infection.

The main features of the published cases of cerebral chromoblastomycosis are noted in Table II. There may be other cases in the literature, although a search has not disclosed any which appear to come in this category. Mariat (1957) suggested that a case which was reported by Wybel (1952) might be an example of chromoblastomycosis: the patient died of a fungal granuloma of the meninges of the cervical part of the

spinal cord; cultures were not obtained, and on morphological grounds Wybel had tentatively identified the organism as an aspergillus, which he suggested might have been introduced into the theca accidentally when penicillin was injected three years earlier during treatment of pneumococcal meningitis. The available evidence does not seem to warrant a diagnosis of chromoblastomycosis in this case.

A case of meningitis and ependymitis described by Moore, Russell, and Sachs (1946) is possibly relevant to this study: their patient was a farmer, and they considered that a dark fungus present in the lesions was *Ustilago zeæ*, a mould which causes corn smut. The patient had had a craniotomy four years or so before his last illness—the operation was undertaken for cerebellar symptoms and the findings were interpreted as "chronic cystic arachnoiditis"; no biopsy specimen was taken. The craniotomy wound had drained for four months after the operation, and during this time the patient had returned to his work, which included husking corn: Moore and his associates suggested that the fungus might have gained access to the tissues through contamination of the drainage tract at that time, or alternatively by way of the gastro-intestinal tract. Cultures were not taken, and the identification of the organism as *Ustilago zeæ* was based on its morphological characteristics, including the presence of sprout mycelium and of spores with spiny or warty excrescences like those of smut fungi. Although the authors dismissed the possibility of chromoblastomycosis their grounds for doing so were clearly based on the then current assumption that the organisms which cause chromoblastomycosis occurred only in chlamydospore form in tissues. In fact, all the features which they described and illustrated as suggesting that the fungus was *Ustilago* may be seen in cases of cerebral chromoblastomycosis and were present not only in the lesion in the case reported in this paper (figs. 9 and 10) but also in the sections from Case 9 of Table II which Doctor Mariat made available to me. The possibility of chromoblastomycosis in the case of Moore and his colleagues (1946) therefore seems to be well worth considering, although in the circumstances it has not been included in Table II. The only other case on record in which the diagnosis of "ustilagomycosis" was made is not in any way comparable with theirs: it was a case of acute dermatitis attributable to sleeping in the rain on contaminated soil after working in hot sunshine (Preininger, 1937).

It is just possible that the case of supposed meningeal sporotrichosis reported by Hyslop, Neal, Kraus, and Hillman (1926) was an example of chromoblastomycosis: spores and mycelium were found in the cerebrospinal fluid, and the fungus was found in sections of the meninges *post mortem*, but the cultures were always sterile; the morphological data and the photomicrographs do not particularly suggest chromoblastomycosis, and there is no mention of the organism being pigmented. However, while speculation of this sort generally has little merit the case is noted

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here as another example of an unexplained or equivocal mycotic infection of the central nervous system in which the possibility of chromoblastomycosis, although remote, is not wholly fanciful: certainly this diagnosis should be considered in any comparable cases in the future.

It should be stressed that the lesions of chromoblastomycosis were confined to the brain in all the cases listed in Table II except the case with cutaneous infection (Case 12); however, in 2 cases there was permission to examine only the brain at necropsy (Case 12, again, and Case 3), and in 2 cases there was no necropsy (Cases 9 and 10). Also, the significance of isolating the organism from the middle ear in Case 5 and of finding spores and hyphæ in the lungs in Case 7 remains obscure.

As the chromoblastomycotic nature of the infection was recognized during life in several of the cases tabulated (Cases 4, 5, 9, and 10) and the fungus was isolated but mistaken for a candida in another case (Case 11) it may be anticipated that a proportion of future cases will also be recognized during life. This infection must clearly be considered in the differential diagnosis of any intracranial abscess or granuloma, and the need to be on the lookout for fungi and to adopt appropriate measures to ensure that they will be isolated when present, and not mistaken for contaminants, is obvious. Cultures are essential, not only for complete identification of the fungi but also in order to enable their sensitivity to drugs to be investigated.

Up to now no consistently effective means of treating chromoblastomycosis has been found although the problem has been energetically investigated in cases of the cutaneous infection. The antifungal antibiotic amphotericin B, which has a remarkable effect on a number of other types of deep-seated fungal infection, prevents the growth of the causative fungi of chromoblastomycosis *in vitro* only in concentrations which are several times higher than can be obtained *in vivo* following parenteral administration by the ordinary routes. Costello, DeFeo, and Littman (1959), however, tried the effect of injecting the drug directly into the vicinity of the lesions in a case of cutaneous chromoblastomycosis and obtained a satisfactory result. In view of the seriousness of cerebral chromoblastomycosis it would probably be justifiable to consider intrathecal administration of amphotericin B ("Fungizone for Infusion" [Squibb]) in cases in which the organism is shown to be sensitive to this substance: it should be remembered that little is known as yet about the hazards of giving amphotericin B by this route.

In conclusion, it may be noted that the chromoblastomycoses must be added to the list of fungal infections of the central nervous system—in fact, chromoblastomycosis due to *Cladosporium trichoides*, torulosis (cryptococcal infection), and the mucormycoses due to *Rhizopus* or other phycomycetes form a trio of infections which have a particular affinity for the central nervous system. This affinity distinguishes these three

types of mycosis from all the other deep-seated fungal infections, which only occasionally or incidentally involve the brain or meninges.

SUMMARY

The chromoblastomycoses are infections caused by various related fungi which differ from other pathogenic fungi in being naturally pigmented. Because of their brown or yellow colour the chlamydospores and hyphæ of these organisms are readily seen in preparations of infected tissues, even when unstained. Cutaneous chromoblastomycosis is a disease of hot climates. Cerebral chromoblastomycosis, which usually is due to a species of fungus distinct from those causing the cutaneous infection, occurs in temperate climates as well as in the tropics and subtropics.

A case of chromoblastomycosis of the brain is reported. The patient had never been out of England. The infection appears to have developed as a complication of a cerebral infarct. The infarct had resulted from involvement of a middle cerebral artery in polyarteritis. At the time of the stroke the patient had been on treatment with cortisone for eleven weeks and immediately before that she had had a course of penicillin; a second course of penicillin was given during the three weeks between the stroke and death. The significance of treatment with cortisone and penicillin in relation to the development of the fungal infection is debatable. The source and portal of entry of the infection are not known. No evidence of the infection was found except in the brain.

Fourteen previously recorded cases of cerebral chromoblastomycosis are reviewed in tabular form. The usual manifestations are those of a brain abscess; the lesions are often multiple. Recovery has only once been reported: surgical removal of the lesion, although successful in that case, has usually been unavailing; no effective medical treatment is yet known.

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LEGENDS FOR PLATES

PLATE XV

FIG. 1.—Granulation tissue lining abscess, with multinucleated giant cells. Chlamydospores and segmented mycelium of the fungus are seen in the giant cells and adjacent tissue: their natural brown colour shows clearly. Mayer's hæmalum and eosin. "Kodachrome." ×200.

FIG. 2.—Multinucleated giant cells in the cerebral granuloma, with mycelium and a split chlamydospore (to right of, and just above, the right-hand giant cell). The fungus is unstained. Mayer's hæmalum, without counterstain. "Kodachrome." ×440.

FIG. 3.—Periodic-acid/Schiff preparation showing a field similar to that in fig. 1. The mycelium and chlamydospores show up better than in the hæmalum-eosin preparation. In places the characteristic colour associated with the positive Schiff reaction is modified by the underlying natural pigmentation of the fungus. Mayer's hæmalum counterstain. "Kodachrome." ×110.

FIG. 4.—Mycelium and vesicle-like fungal elements in the necrotic central part of the cerebral infarct. Periodic-acid/Schiff reaction; Mayer's hæmalum. "Kodachrome." ×110.

FIG. 9.—Branching mycelium in granulation tissue lining the cerebral abscess. At the centre of the picture is a pair of stippled bodies of the type described by Morris *et al.* (1946) as echinulate spores of their supposed "*Ustilago*." Methenamine (hexamine)/silver-nitrate stain. "Kodachrome." ×440.

PLATE XV

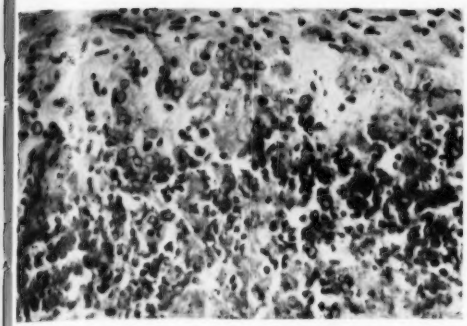


FIG. 1.

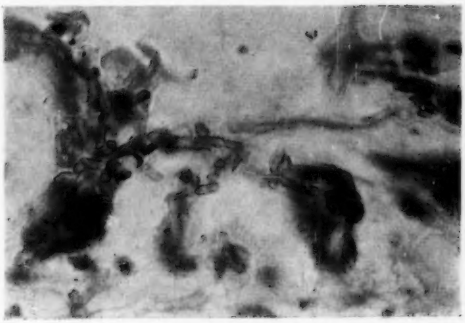


FIG. 2.

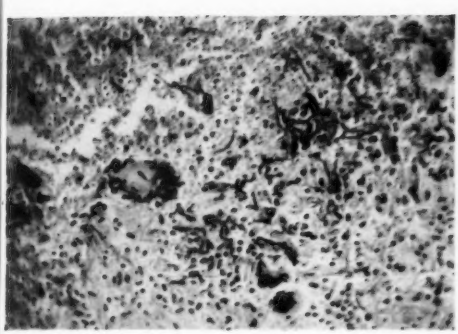
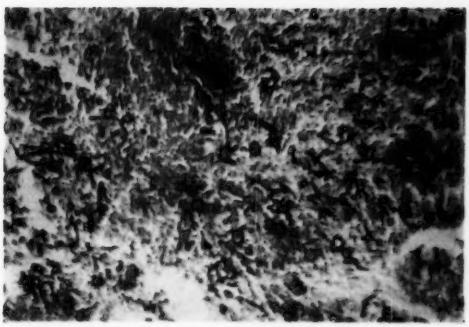


FIG. 3.



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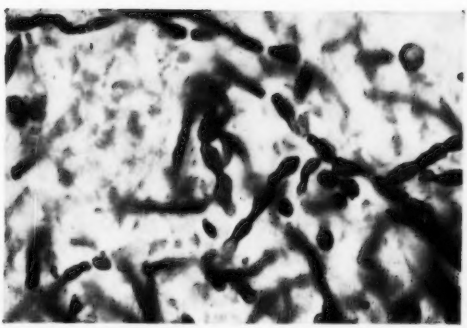

FIG. 9.

To illustrate article by W. St. C. Symmers.

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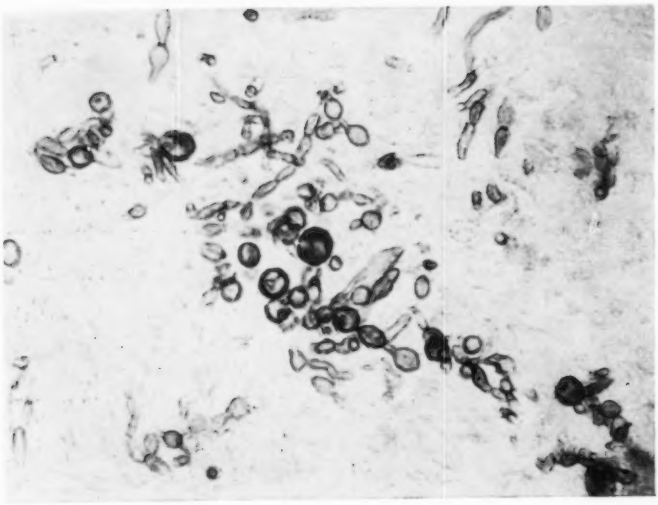

FIG. 5.

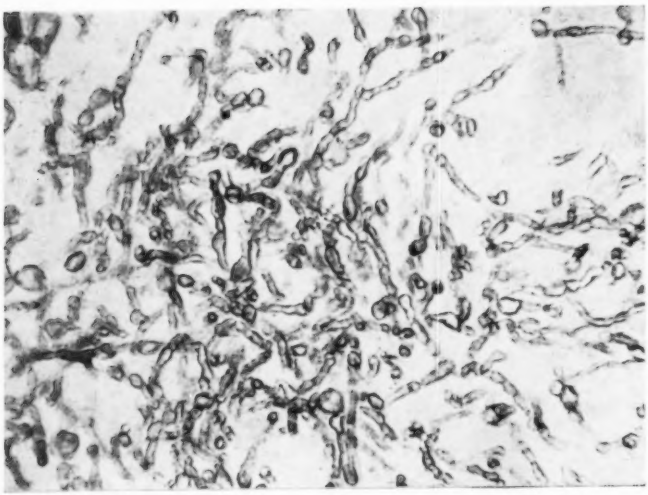

FIG. 6.

To illustrate article by W. St. C. Symmers.

FIG. 7.

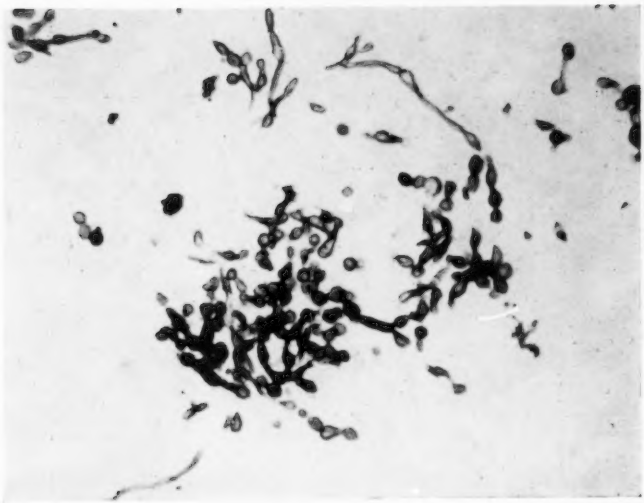

FIG. 8.

To illustrate article by W. St. C. Symmers.

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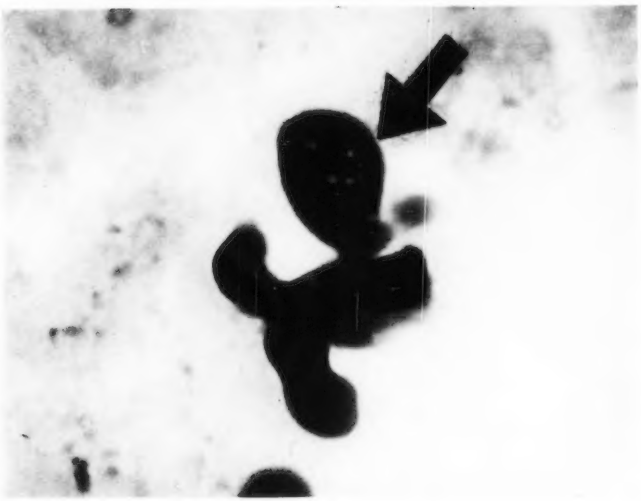

FIG. 10.

To illustrate article by W. St. C. Symmers.

PLATE XVI

FIG. 5.—Unstained section, showing the pigmented, germinating chlamydospores (from granulation tissue lining abscess cavity). Some of the chlamydospores contain septa, as is seen particularly in the largest one in the centre of the picture. ×400.

FIG. 6.—Unstained section, showing the pigmented mycelium. ×400.

PLATE XVII

FIG. 7.—Segmented, branching mycelium and spores (from tissue around abscess). Grocott's modification of Gomori methenamine (hexamine)/silver-nitrate stain. ×400.

FIG. 8.—Segmented, branching mycelium and spores of *Candida albicans* for morphological comparison with the organism causing cerebral chromoblastomycosis. This picture is from a section of kidney from an experimentally infected rabbit: I am indebted to Dr. H. I. Winner for providing the tissue. Methenamine (hexamine)/silver-nitrate stain. ×400.

PLATE XVIII

FIG. 10.—Another "echinulate" body (arrowed). Methenamine (hexamine)/silver-nitrate stain. ×1,650.

VARIATIONS IN THE RESPONSES EVOKED BY LIGHT ALONG THE SPECIFIC PATHWAYS

BY

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IN recent years, a number of workers have drawn attention to the possible existence of a central control mechanism in the transmission of specific afferents (Hagbarth and Kerr, 1954; Hernández-Peón and Scherrer, 1955; King, Naquet and Magoun, 1957; Hernández-Peón, Guzmán-Flores, Alcaraz and Fernandez-Guardiola, 1956; Jouvet and Hernández-Peón, 1957; Buser, 1957).

Various hypotheses have been formulated as to the level at which this control takes place. The hypothesis that a control exists at the level of the first peripheral relay has obtained the greatest support (Jouvet and Hernández-Peón, 1957).

The results which we report here confirm the complexity of the problem, at least in so far as the visual pathways are concerned.

TECHNIQUE

The experiments were carried out on non-anæsthetized cats which were immobilized by curare (Flaxedil), the preparation (tracheotomy and craniotomy, etc.) having been performed under ether anæsthesia.

Recordings from subcortical structures along the specific visual pathways (optic chiasma and lateral geniculate body) were carried out by means of concentric bipolar electrodes inserted by stereotaxis with the Horsley-Clarke stereotaxic apparatus.

Corticography was carried out by means of chlorulated silver electrodes, applied directly on to the cortex and using either monopolar or bipolar recording.

An Alvar Reega 10-channel electro-encephalogram (EEG) apparatus was employed.

[1]Working with a fellowship from the Wellcome Trust Foundation, while on study leave from the London Hospital.

[2]Working with a bursary from the French Government while on study leave from the University of Mexico.

In certain cases the potentials evoked by light were photographed by a camera on an oscilloscope. The camera was a Grass model and the oscilloscope Cossor.

Photic stimulation (with single flashes) was carried out by a stroboscope Soneclat Alvar in a soundproof room in total darkness.

Stimuli of "arousal" were delivered either by nociceptive stimuli (pinching the tail or electrical stimulation of the sciatic nerve) or by direct electrical stimulation of the reticular formation of the mid-brain by means of concentric electrodes.

After having worked during the first part of the experiment with a reacting pupil, we obtained maximal and fixed pupillary dilatation by applying atropine or homatropine directly into the eyes.

RESULTS

I. *Variations in the Evoked Visual Responses Before Atropine* (*see* fig. 1A).

(*a*) *Relationship between variations in pupillary diameter and the state of synchronization or desynchronization of the cortex.*—Whenever cortical activity accelerates (showing rhythms of fast frequencies, a so-called desynchronized record indicating an "activated" cortex) the pupil dilates and this dilatation lasts throughout the period of desynchronization.

When cortical activity tends to slow down again (showing a more or less synchronized activity associated with spindles and slow waves) the pupil becomes progressively smaller and remains in myosis throughout the time that the preparation lasts synchronized.

This relationship between the diameter of the pupil and the activity of the cortex exists whether the acceleration of cortical rhythms takes place spontaneously or in consequence of direct or indirect stimulation of the reticular formation.

(*b*) *Variations in the evoked response at different levels of the specific pathways during the state of cortical desynchronization.*—The amplitude of the evoked response recorded from the optic chiasma and the lateral geniculate body increases whenever the cortex is activated (desynchronized). Simultaneously, however, the amplitude of the evoked response recorded from the specific (i.e. visual) cortex diminishes and its morphology changes. The positive phase diminishes slightly in amplitude or remains the same whilst the negative slow wave disappears almost entirely.

(*c*) *Variations in the evoked response at different levels of the specific pathways during the state of cortical synchronization.*—When cortical activity slows down again the evoked response recorded from the optic chiasma and the lateral geniculate body diminishes in amplitude. Simultaneously, however, on the specific visual cortex the amplitude of

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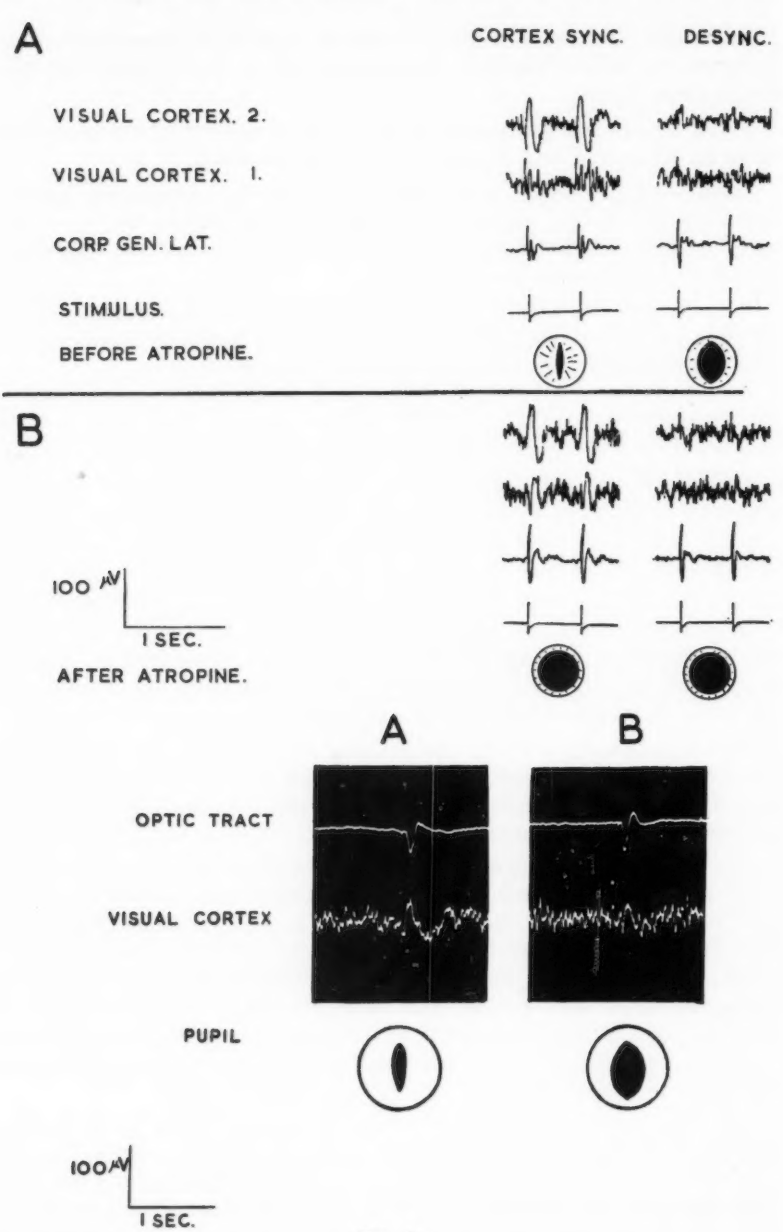
A
CORTEX SYNC.
DESYNC.
VISUAL CORTEX. 2.
VISUAL CORTEX. 1.
CORP. GEN. LAT.
STIMULUS.
BEFORE ATROPINE.
B
100 μV
1 SEC.
AFTER ATROPINE.
A
B
OPTIC TRACT
VISUAL CORTEX
PUPIL
100 μV
1 SEC.

FIG. 1.

the evoked potential increases again. This modification particularly affects the negative component wave which becomes of very large amplitude and may be followed by a slow after-discharge, taking on at times the appearance of a spindle.

II. *Variations in the Evoked Visual Responses after Local Application of Atropine* (*see* fig. 1B).

When the pupil is fixed in complete mydriasis, there is no longer any relationship between its diameter and the state of relative synchronization or desynchronization of the cortex.

The evoked potential recorded from the chiasma and the lateral geniculate body is of very large amplitude and does not vary whatever the electrical activity of the cortex, whether synchronized or desynchronized.

The response on the cortex shows the same variations as before the application of atropine, provided that the experimental conditions do not change (blood pressure, relative hypoxia, etc.).

Summary and Conclusions

The authors confirm (1) the existence of a relationship between the diameter of the pupil and the degree of activation of the cerebral cortex in the cat under Flaxedil. This agrees with the work of Bonvallet, Dell and Hiebel (1954). (2) They also confirm previous results which have demonstrated that the amplitude of an evoked cortical potential diminishes during desynchronization, which may be described as a masking effect (Bremer, 1952).

These results permit the following conclusions:

(1) The amplitude of an evoked response recovered from the optic chiasma and lateral geniculate body depends more on the conditions of illumination of the retina (that is to say on the diameter of the pupil) than on the conditions of activation or non-activation of the cortex.

(2) On the other hand, the amplitude and morphology of the evoked response recovered from the specific visual cortex depend much more on the state of relative synchronization or desynchronization of the whole of the cortex than on the amplitude of the evoked potential in the chiasma and the lateral geniculate body.

These findings go towards proving that there exists a control of specific afferents (if one admits that the amplitude of an evoked potential has a quantitative value) (Crighel, Gratzian and Naquet, 1958). They seem in opposition to the studies which tend to point to the idea that the reticular formation exerts an inhibitory influence at the level of the first sensory relay (Hernández-Peón, Guzmán-Flores, Alcaraz and Fernandez-Guardiola, 1956), at least in so far as the visual pathways are concerned

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and under our experimental conditions. They are, on the other hand, in accordance with results which have demonstrated (at least to a large extent) that this control takes place after the thalamic relay, whether it be a matter of visual afferents (Buser and Borenstein, 1957) or of somatic afferents (King, Naquet and Magoun, 1957). Similar results have recently been reported with auditory afferents (Buser and Borenstein, 1959).

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ELECTRICAL ACTIVITY OF THE CEREBRAL CORTEX OF THE UNANÆSTHETIZED CAT DURING ATTENTIVE BEHAVIOUR

BY

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The Department of Neurology and Neurosurgery and the Montreal Neurological Institute, McGill University

INTRODUCTION

SENSORY inflow into the nervous system may be controlled in a number of ways. Closure of the eyelids, for example, greatly reduces the afferent input necessary for pattern vision and rubbing or tickling the skin behind the shoulder of a dog is followed by rhythmic scratching movements of the hind-limb (Haycraft, 1890; Sherrington and Laslett, 1903) which would tend to remove the source of the stimulus. Reflex contraction of the intra-aural muscles to loud sounds by increasing the tension on the tympanic membrane, reduces its movement and so may effect some control over the intensity of the acoustic inflow (Wiggers, 1937). The loading or bias of muscle spindles and hence the discharge from them into the spinal cord are under the fine control of supraspinal centres through the γ motor neurons (Kuffler, Hunt and Quilliam, 1951; Eldred, Granit and Merton, 1953). In this way muscle spindles may be adjusted to be continuously under slight tension and thus in a state of maximum sensitivity to stretch.

Other mechanisms (Hagbarth and Kerr, 1954; Kerr and Hagbarth, 1955; Galambos, 1956; Dawson, 1958) may supplement the activity of those described above by modulating the sensory inflow. However, it does not follow that centrally controlled inhibitory activity serves only to block or exclude signals. Indeed where inhibitory mechanisms operate in the afferent pathway, as at the retina (Kuffler, 1952) and, possibly in the cochlear nucleus (Allanson and Whitfield, 1956) one of their effects may be to improve sensory contrast.

A central mechanism capable of regulating the threshold of sense receptors has been postulated (Horn, 1953), whereby sensory signals into the central nervous system may, under appropriate behavioural conditions, be augmented by descending facilitation or attenuated by descending inhibition. Adrian (1954) suggested the possibility that some

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controlling mechanism might operate on the transmission of afferent signals at a subcortical level so that when we "attend" to a sound ". . . and are unaware of contacts and pressures, it is because the auditory signals reach the cortex and the tactile signals do not." Hernández-Peón, Scherrer and Jouvet (1956) attempted to test a similar hypothesis. They found that click evoked responses in the dorsal cochlear nucleus of the unanæsthetized cat were decreased in amplitude during "attention" to a non-auditory stimulus. It was concluded that, "If this sensory inhibition during attentive behaviour, as demonstrated in the auditory pathway, occurs in all other sensory paths, except the ones concerned with the object of attention, such an inhibitory mechanism might lead to the favouring of the attended object by the selective exclusion of incoming signals." These experiments were subsequently extended to the visual system (Hernández-Peón, Guzmán-Flores, Alcarez and Fernández-Guardiola, 1957). It was found that when an animal's "attention" was attracted by non-visual stimuli, photically evoked responses recorded in the visual cortex, lateral geniculate body and optic tract, were reduced in amplitude. These results were cited as additional evidence in support of the hypothesis that during "attention" an inhibitory mechanism ". . . appears to restrict sensory meaningful activity in those afferent pathways occupied by the subject of attention. The span of conscious sensory perception at a given moment is limited by blocking of sensory messages at the periphery . . . " (Hernández-Peón *et al.*, 1957).

There are, however, a number of points in these experiments that require clarification. For example, reduction in amplitude of an evoked potential does not necessarily signify that signals are being "blocked." If the units composing the response were dispersed in time the amplitude of the evoked potential would appear reduced but the total input need not be diminished. In addition it is not clear from the published results (Hernández-Peón *et al.*, 1957) how attentive behaviour was assessed, but when monitoring activity in the visual pathway to a flash of light, the cat's "attention" was attracted, among other stimuli, by a call or by sardine odour blown into the cage. When a cat is called it usually "attends" by *looking* toward the source of the voice: when fish odour is blown into the cage it "attends" by sniffing and *looking* toward the source of the odour. It is thus possible that "attention" to a non-visual stimulus resulted in the cat searching the visual sensory field for the source of the stimulus. A similar criticism could be made of the studies of the auditory system (Hernández-Peón *et al.*, 1956) when "attention" was attracted to a visual stimulus, a mouse. It is not inconceivable that when a cat looks at a mouse it also listens. The above experiments, therefore, do not exclude the possibility that depression of an evoked response occurs in the modality actually being used for examining the sensory field. One of the objects of the experiments described in the present paper was to

investigate this possibility. Thus the experiments were designed to determine what changes, if any, occur in the cortical response to flash when the cat's behaviour is directed to an object in the visual sensory field. In a further series of experiments any changes in the evoked response to flash were observed when the animal's behaviour was directed to an auditory stimulus in such a way that any searching of the visual sensory field could be taken into account. A report is also given of changes in the cortical response to clicks in one cat, when its behaviour was directed to an object in the visual field.

Materials and Methods

Seven cats were used. In six of them stainless steel monopolar electrodes of approximately 1 mm. tip diameter were placed subdurally on the visual cortex (lateral gyrus) when the cat was anæsthetized with pentobarbitone. The reference electrode was screwed into the frontal bone. Leads from the electrodes were delivered through a hole in the skin over the neck and soldered into a socket strapped to the animal's back (Bradley and Elkes, 1953). Several days after recovery from the anæsthetic the cat was placed in a shielded wooden cage 3 ft. × 3 ft. × 2 ft., the front of which consisted of a sliding sheet of Perspex. In front of the Perspex window and at a distance of about one foot was placed a stroboscope which delivered flashes approximately once every two seconds with a duration and intensity of approximately 1 millisecond (m.sec.) and 1 lambert respectively. To one side of the box was screwed a loudspeaker through which could be delivered tones from an audio-frequency oscillator and clicks generated by a Grass stimulator. Electrical activity from the cortex was fed into a Tektronix Type 122 pre-amplifier with high-frequency response set at 40 kc./s. and low frequency response at 0·8 cycles per second (c./s.). The signals were then displayed on a Dumont Type 322 dual beam oscilloscope and filmed. A silver plate electrode was secured to the fore-limbs so that an electric shock could be delivered by completing a circuit through the cat and the copper mesh floor of the cage. The intensity of the shock was varied for each animal, being just sufficient to cause an observable behavioural response. The animal was free to move about the box, the leads from the electrodes being sufficiently long not to impede movement. During an experiment the stroboscope was switched on when the animal was put into the cage and flashes delivered throughout the trial. The cat was not continuously exposed to the light for more than two hours at a time, in order to minimize any attenuation of the evoked potential which might occur following prolonged repetitive presentation of the stimulus (cf. Galambos, Scheatz and Vernier, 1956).

A mouse was used to orientate the cat's behaviour to the visual sensory field. For about two minutes at each trial the mouse was placed outside the cage between stroboscope and cat, separated from the latter by the Perspex sheet. At this time 20 or more evoked responses to flash were recorded. Ten of these responses were selected at random for measurement, together with 10 control responses from the resting, relaxed animal, recorded immediately before introduction of the mouse. A trial was considered valid only if the cat's position relative to the stroboscope was substantially unchanged during experimental and control periods. Some movement, however, was inevitable and test runs were made to determine whether any observed differences between experimental and control trials were due simply to (*a*) changes in the cat's position relative to the stroboscope and (*b*) muscular movements as the cat watched the mouse. Records were taken of photically evoked potentials to flash in the relaxed animal (*a*) when its position relative to the stroboscope was

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varied through a wide angle, and (*b*) when it moved spontaneously to roughly the same extent as when it was watching the mouse.

In order to direct the animal's behaviour away from the visual field a conditioning procedure was adopted, using tones as conditioned stimuli and a light electric shock applied to the fore-paws as the unconditioned stimulus. The tones were in the frequency range of 2,000 to 7,000 c./s. Single tone pips in the intervals between flashes were delivered through the loudspeaker. In each trial 3–10 tone pips were delivered between consecutive flashes and then the animal shocked. The number of tones delivered in any trial was varied at random so that the animal could not predict after which tone the shock would be delivered. When the tone had become a conditioned stimulus (after 5–10 runs) reinforcement with shock was only made once in every fifth to eighth trial. This reinforcement interval was also varied indiscriminately to minimize the chances of the animal successfully predicting when it was likely to be shocked. Records were made of photically evoked responses during the conditioning trials and compared with the control responses recorded immediately prior to the delivery of the tones at a time when the cat appeared to be relaxed.

Records were measured in the following way. A magnified image (× 10 linear dimensions) was projected on to a sheet of graph paper. The electrocorticogram (ECoG) in the 500 m.secs. before the onset of an evoked response, was measured to give an index of the background cortical activity. This activity was characterized by slow oscillations of the ECoG, referred to as the major waves, and by higher frequency minor waves which appeared as ripples superimposed upon the major waves. A horizontal line was fitted to the image of the ECoG, about which by inspection the crests and troughs of the major waves appeared equally distributed. A pencil line was then drawn through the image of the waves and the number of complete sinusoidal oscillations in 500 m.secs. counted. The amplitude of all the crests and troughs above and below the line was measured and the average value so calculated gave the mean amplitude of the major waves of the background ECoG. This line was continued through the image of the evoked response and was used as the base-line about which the amplitude of the surface positive and surface negative components of the evoked response were measured. The amplitude and frequency of the oscillations in the 500 m.secs. following the second wave of the evoked response were determined in the same way.

The mean value was calculated for each of the ten sets of data measured from experimental and control records. These means for each animal were tabulated and the significance of any differences between experimental and control conditions obtained by applying a paired t test (Snedecor, 1938). Wherever a value is given in the results for the standard deviation, it refers to the standard error of the mean.

In one animal a monopolar electrode was placed on the auditory cortex and a click delivered through the loudspeaker approximately once in two seconds. The evoked response was recorded in the relaxed animal and compared with the response when the cat's behaviour was directed toward a mouse. The records were single frames containing about 500 m.secs. of trace, including the evoked response. The amplitude of the evoked response was measured and the significance of any differences between experimental and control runs estimated by applying an unpaired t test (Snedecor, 1938).

RESULTS

A. *Visual System*

(1) *General considerations of the electrical activity of the visual cortex.*— Resting records (fig. 1) were taken when the cat, relaxed and usually prone, lay facing the stroboscope. These records were filmed only after

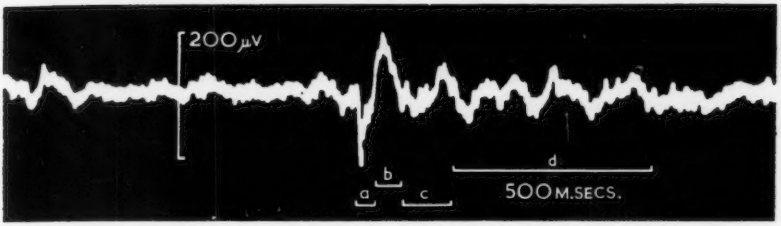

FIG. 1.—Evoked response to flash recorded at the visual cortex (lateral gyrus) in the unanæsthetized, relaxed cat. In this and in all subsequent figures, upward deflections are negative. (*a*) = surface positive component and (*b*) = surface negative component of the primary wave; (*c*) = secondary wave; (*d*) = tertiary component of the evoked response.

the cat had remained in one position for several minutes at least, when its breathing was regular, claws sheathed and pinnæ relaxed. The mean frequency of the ECoG in the 500 m.secs. prior to the onset of the evoked response to the photic stimulus (the background ECoG) was 8·2 ($\pm$0·3) c./s. and the mean amplitude 40 ($\pm$1·8) micro-volts (μV.). The flash artefact was not always clearly seen on the trace; so the latency of the cortical response was not determined. The evoked response was made up of several components (fig. 1). The first consisted of a surface positive followed by a surface negative oscillation, jointly referred to as the primary wave of the response (fig. 1, a, b). The mean amplitude of the surface positive component of the wave was, in the present study, 123 ($\pm$13·6) μV. with a duration of 29$\pm$3·5 m.secs. Surface positive spikes on the descending limb of the positive wave were not invariably present and were not measured. The surface negative deflection was smaller than the surface positive wave, with a mean amplitude of 70 ($\pm$4·7) μV.: its duration was longer, however, with a mean value of 63 ($\pm$9·1) m.secs. Following the return of the trace to the base line another surface positive–surface negative wave was described (fig. 1, c). This deflection is referred to as the second wave of the response and commenced 92$\pm$9·7 m.secs. after the onset of the primary wave with a peak to peak amplitude of 80$\pm$6·7 μV. The frequency of the waves in the succeeding 500 m.secs. (7·6$\pm$0·4 c./s.) was not significantly different ($P > 0·2$) from the frequency of the oscillation in the half-second preceding the evoked response. The mean amplitude of 50 ($\pm$3·6) μV., however, was 25 per cent greater ($P < 0·02$) than the mean amplitude of the background ECoG. It is thus apparent that the magnitude of the oscillations in the 500 m.secs. following the second wave of an evoked response does not return to the background ECoG value. These waves are therefore referred to as the tertiary components of the response (fig. 1d).

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It is, of course, possible that the delineation of the second wave of an evoked response from the tertiary waves is entirely artificial. Evidence derived from the present study, however, is not consonant with this view.

TABLE I.—ELECTRICAL ACTIVITY OF THE VISUAL CORTEX OF THE UNANÆSTHETIZED CAT

Values given in columns are means ± standard error of means for experimental animals relative to control level of 100. Mean values in ordinary type are not significantly different from control values at the 5 per cent limits of confidence: data given in roman differ from control values significantly, between 2 and 5 per cent confidence limits. Experimental data which differ from control values with a significance of $P<0{\cdot}02$ are indicated in heavy type.

	Orientation to mouse		*Positive orientation to tone*	
Cortical activity	*Positive*	*Negative*	*Early conditioning*	*Late conditioning*
EVOKED RESPONSES				
Primary wave				
Surface positive				
Amplitude ..	**73 ± 2·7**	103 ± 6·6	**79 ± 5·5**	98 ± 8·6
Duration ..	**80 ± 3·5**	104 ± 4·4	**81 ± 4·8**	102 ± 7·4
Surface negative				
Amplitude ..	**79 ± 6·0**	*114 ± 4·1*	84 ± 9·7	110 ± 9·6
Duration ..	83 ± 10·5	97 ± 5·2	98 ± 6·4	93 ± 3·3
Secondary wave				
Amplitude	**81 ± 5·1**	115 ± 11·0	**66 ± 6·7**	88 ± 7·2
Tertiary waves				
Amplitude	**49 ± 3·6**	156 ± 40·6	**60 ± 9·6**	85 ± 7·1
Frequency	97 ± 10·0	119 ± 28·3	92 ± 12·0	95 ± 6·7
BACKGROUND ECoG				
Amplitude	**51 ± 6·3**	108 ± 7·5	**58 ± 11·0**	**74 ± 8·7**
Frequency	88 ± 3·4	112 ± 9·9	93 ± 17·0	106 ± 7·8

It is true, as may be seen in Table I, that with the exception of data in the last column, whenever the amplitude of the background ECoG is reduced, the amplitude of the secondary and tertiary waves of the evoked response are also reduced. It is possible, however, to obtain conditions in which the amplitude of the ECoG and of the tertiary waves are diminished, but in which the secondary wave of the evoked response is not attenuated. Tracings showing these characteristics were found in the course of examining records in several animals. Data from three of these animals were selected for detailed measurement. In two of the cats the records were obtained immediately after a slight shock had been delivered to the limbs and in the third, as the cat sat vigorously grooming itself. It was found that when the mean amplitude of the background ECoG was reduced by 52 per cent compared with the control value, the mean amplitude of the tertiary waves was reduced by 56 per cent. Under the conditions of the present study it appears therefore, that the tertiary waves of the evoked response depend for their presence or absence on

the activity of the background ECoG. When the latter is characterized by low voltage oscillations, the tertiary waves are invariably depressed. It has been shown above that it is the amplitude, not the frequency of the tertiary waves which changes compared with the waves of the resting ECoG. This suggests that the tertiary component of the evoked response is a reinforcement of the basic rhythm of the ECoG and would therefore be expected to change as the character of the ECoG changes, a requirement that is fulfilled in the present study.

It is apparent from Table I, columns 1 and 3, that when the ECoG is markedly reduced in amplitude the secondary wave is also reduced as is the surface positive component of the primary wave.

In the absence of other information it might be concluded that these changes in the evoked response were a consequence of the associated changes in the background ECoG. In the records from the three animals mentioned above, however, reduction in amplitude of the ECoG by 52 per cent (a greater reduction than any recorded in Table I) was not associated with any significant reduction in amplitude of the secondary wave, or of the surface positive and negative components of the primary wave. Indeed in the records from the three animals, the mean control amplitude of the surface negative wave was 73 μV. compared with the mean value of 76 μV. recorded when the waves of the ECoG were flattened. These observations raise the possibility that reduction of the primary and secondary waves in the experiments described below may be due to some factors other than, or in addition to, those responsible for reducing the voltage of the ECoG. In addition it may be seen (Table I) that changes in amplitude of the second wave follow more closely changes in the surface positive than the surface negative component of the primary wave. This observation is of some interest in the light of Brazier's (1958) finding that the secondary wave of a photically evoked response is present in the region traversed by the geniculocortical radiation to the lateral gyrus, but is not present in the lateral geniculate body.

There was considerable variation in both amplitude and duration of the evoked potentials in the resting animal (fig. 2). Marked differences in magnitude were observed even in consecutive responses and when there was no objective evidence of any change in the cat's behaviour. The

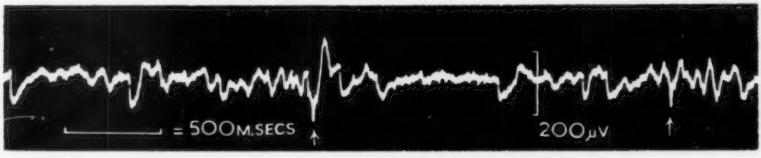

FIG. 2.—Spontaneous variation in the cortical response to consecutive flashes of light in the relaxed animal. Arrows indicate position of evoked responses.

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range of variation of individual responses was sometimes as great as or greater than the observed differences between mean values under control and experimental conditions. The magnitude of this spontaneous variation underlines the need to quantify results when looking for any differences between evoked responses in the unanæsthetized cat and makes hazardous any attempt to single out a representative response, in the absence of such information.

(2) *Positive and negative orientation to mouse.*—On the first few occasions that a mouse was presented, the cat responded in a fairly characteristic way. It looked toward the mouse, the pinnæ were drawn forward and it moved to the Perspex sheet separating it from the mouse. The cat patted the screen and tried to force its fore-paws under it: the claws were unsheathed, there was pilo-erection and pupillary dilatation. Often, the cat would then draw back from the Perspex window, arch its back and walk up and down the box with its gaze fixed on the mouse, returning occasionally to try to push the paws under the screen. This excited behaviour (Stage 1) was present, in varying degrees of intensity, in some animals even during the seventh and eighth presentation of the mouse. During subsequent presentations the cat was much less excited and made few attempts to push its paws under the window, its claws remained sheathed, there was little or no pilo-erection or pupillary dilatation. The pinnæ were pricked forward, however, and the cat watched the mouse as it ran along the ledge on the outside of the box. The times at which this phase of behaviour (Stage 2) appeared was variable and seemed to depend on how quickly the cat learned that it could not reach the mouse. The behaviour which characterises Stages 1 and 2 is referred to here as positive orientational behaviour. The final stage (Stage 3) of this series of experiments was reached when the cat showed no behavioural evidence of interest in the mouse and did not follow its movements along the ledge. The cat's pinnæ were not drawn forward and it showed no response when the mouse was withdrawn. This phase of behavioural indifference is referred to as the stage of negative orientational behaviour.

Throughout the course of Stage 1 there was a great deal of movement and evidence of considerable sympathetic activity. Any changes in cortical activity observed during this stage could be attributed to these motor and autonomic accompaniments of the positive orientational response. There was much less movement and much less evidence of sympathetic activity during Stage 2 and it is data recorded during this Stage that were analysed and are reported in Table I, column 1. The records taken during Stage 1 show changes similar to those of Stage 2, but, if anything, of greater magnitude.

The oscillations of the background ECoG were reduced in amplitude during behavioural Stage 2, though their frequency remained unchanged compared with control conditions. The amplitude of all components of

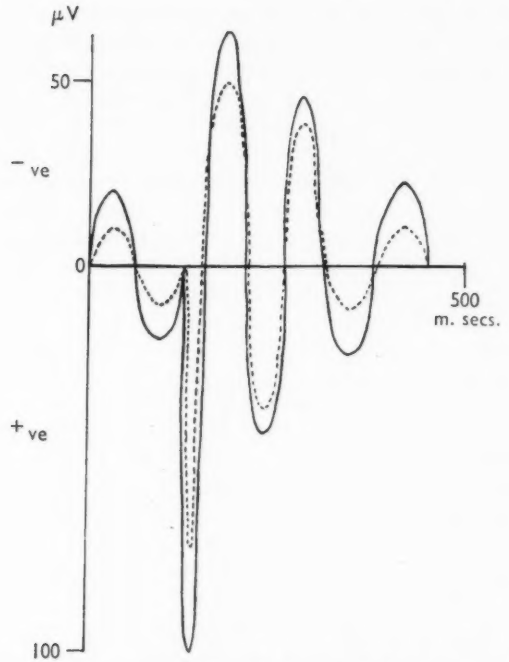

FIG. 3.—Diagrammatic representation of mean evoked response to flash recorded at the visual cortex in 5 unanæsthetized cats. Continuous line = control response in relaxed animal; broken line = response as cat watched mouse. Differences in duration of surface positive component of primary wave not shown. In this figure and in figs. 4 and 5, duration of secondary wave is approximate, while differences in amplitude are shown only if significant ($P<0{\cdot}02$). The first and last waves in these figures represent respectively the mean duration and amplitude of waves in the 500 m.secs. preceding the response and following the secondary wave.

the evoked response was also significantly reduced compared with control values. These results are illustrated diagrammatically in fig. 3. Similar changes were observed in bipolar records from one animal from which both monopolar and bipolar recordings were taken. A measure of the total current generated in the production of the primary response is given by the area beneath the wave. An index of this area is given by the width and height of the wave and both these measurements are required to determine whether or not there is a significant reduction in the total generating current. It was found that in fact the mean duration of both surface positive and surface negative components of the primary wave were reduced, though the degree of reduction did not quite reach statistical significance in the case of the surface negative component. Hence it is not reasonable to attribute the reduced amplitude of these waves to a

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wider temporal dispersion of the units composing them.

When the mouse was presented but elicited no apparent orientational response from the cat (Table I, column 2) the background ECoG showed no flattening. There was no evidence of a depression of amplitude of the evoked response; the mean values for all components tended to be slightly greater than that of the resting controls. This increase reached statistical significance in the case of the surface negative wave of the primary response.

Changes in the alpha rhythm of man during attention to vision (Adrian, 1944) parallel the ECoG changes described here. In human subjects the alpha rhythm appears in the cerebral cortex when attention is not directed to the visual fields and disappears when it is.

It was inevitable, even in Stage 2, that some movement of the cat's head or ears or limbs took place as it watched the mouse, otherwise it would have been difficult to know whether or not the cat was interested in the mouse. Though this movement was slight the possibility must be considered that it was this movement alone, which by e.g. a proprioceptive discharge leading to occlusion of the visual signals, was responsible for the changes in evoked responses observed during positive orientational behaviour. Records were therefore taken of photically evoked potentials when the relaxed cat moved to about the same degree as, or slightly more than, in Stage 2 of the positive orientational response. The data, which refer only to the primary and secondary waves, are based on records from three cats of which two were moving head and limbs and the third washing itself vigorously. There were no significant differences in the size of these waves under stationary and moving conditions; so depression of the evoked response during positive orientational behaviour is probably not due to the accompanying muscular activity.

Other factors which could be held responsible for the decrease in amplitude of the evoked responses are: (*a*) change in position of the cat's head relative to the stroboscope; (*b*) pupillary constriction consequence on accommodation as the cat looked at the mouse. In respect of (*a*) care was taken that records were made only when the cat maintained its resting position relative to the stroboscope following introduction of the mouse into the box. Nevertheless the cat did move its head through an angle of up to about 90 degrees as its gaze followed the mouse's movements. In a preliminary experiment it was found that movement of the head within an arc of approximately 160 degrees did not effect the size of the evoked response in the resting animal. Pupillary changes which occurred on accommodation were small and are unlikely to be responsible for the marked changes in magnitude of the evoked response observed during Stage 2. Certainly the much larger pupillary changes (dilatation) which occurred during Stage 1 had no observable effect on the evoked response.

(3) *Orientation to tone.*—No definite orientational response to the tones was observed in the first two or three trials, each of which was succeeded by a small shock. On receiving the shock, the animal jumped slightly or lifted the shocked limb and usually moved to another part of the cage. After the third or fourth trial, at the onset of the tones the pinnæ were pricked up and the cat often rose from its resting position and always looked intently round the cage as if searching for some visual cue associated with the tones. This behaviour was continued in any one trial as long as the tone pips were delivered and was terminated almost as soon as the animal was shocked. The phase of conditioning characterized by this behaviour is referred to as the stage of early conditioning. Later

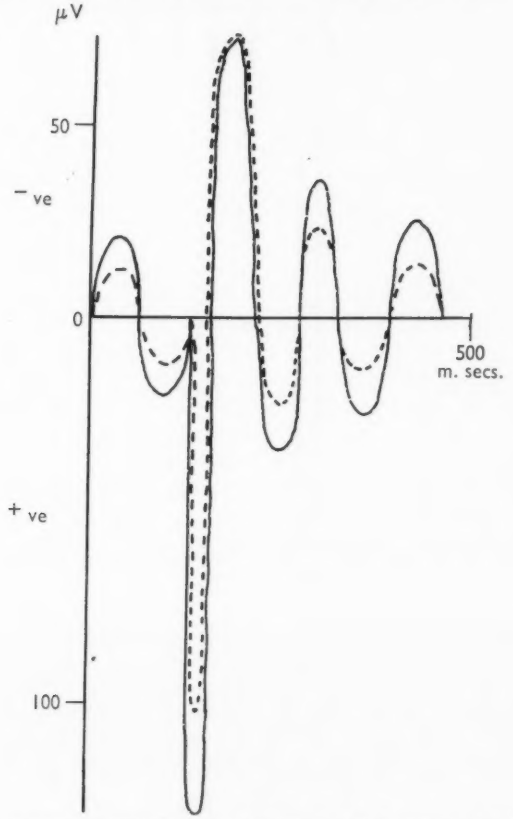

FIG. 4.—Diagrammatic representation of mean evoked response to flash recorded at the visual cortex in 6 unanæsthetized cats. Continuous line = control response in relaxed animal; broken line = response during early stage of conditioning to a tone.

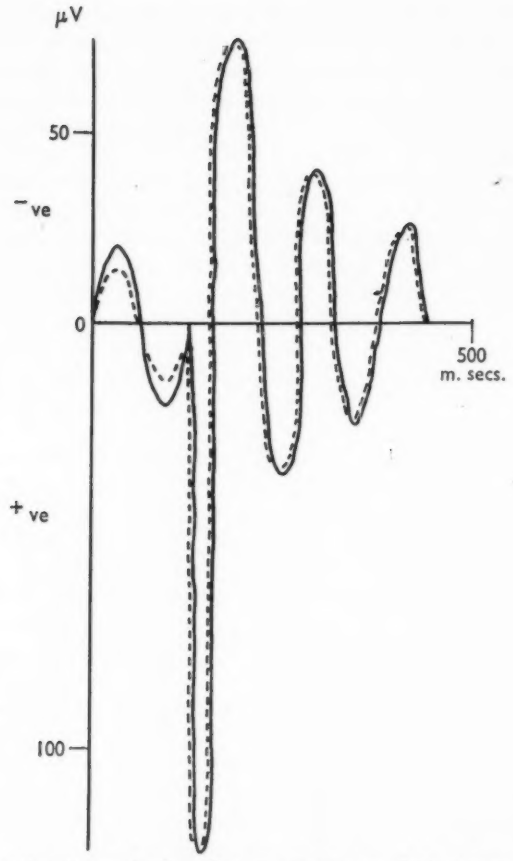

FIG. 5.—As in fig. 4 but broken line = response to flash during late stage of conditioning to a tone.

on, following the tenth to fifteenth trial, the visual searching behaviour gradually ceased to be a component of the response to the tones, and by about the twenty-fifth trial was entirely absent. At this time the cat responded to the tones by flicking its ears, contracting its face muscles and shifting its limbs. Occasionally during the tones the cat moved from its resting position to sit in another part of the cage. This phase is referred to as the stage of late conditioning.

The changes in electrical activity of the visual cortex during the phase of early conditioning are summarized in Table I, column 3. These data are derived from records in which the animal did not move bodily across

the cage, but showed a marked visual searching component in its behavioural response to the tones. The amplitude of the background ECoG was markedly reduced, though there was no change in frequency of the rhythm. The surface positive component of the primary wave was reduced in amplitude and its mean duration diminished by 19 per cent. There was no significant change compared with control conditions in the amplitude of the surface-negative wave although its mean value was reduced. The second wave of the evoked response was diminished by 34 per cent and the mean amplitude of the tertiary waves by 40 per cent. These results are illustrated diagrammatically in fig. 4.

The data measured from records taken during the phase of late conditioning are illustrated diagrammatically in fig. 5, and summarized in Table I, column 4. The records were taken during a trial when the cat lay fairly still throughout the time the tones were being delivered. During this phase of conditioning the animal showed no observable sign of visual searching behaviour in its response to the tones. The background ECoG was significantly reduced in amplitude. All the other parameters measured show no statistically significant differences from the corresponding values measured under control conditions.

B. *Auditory System*

The present study was intended primarily to observe changes in the activity of the visual cortex during various controlled changes in the cats' behaviour. In one animal, however, a monopolar electrode was placed on the primary auditory cortex. Because the results obtained are of some interest they are reported here. The activity of the auditory cortex was monitored by the evoked response to a click. The main disadvantage of filming single frames of the evoked response, with the loss of background ECoG activity, was partly offset by the slightly faster sweep speed used. In this way it was possible to distinguish the small spike on the descending limb of the positive deflection of the primary wave (fig. 6).

FIG. 6.—Evoked responses to successive click stimuli recorded from the auditory cortex (anterior ectosylvian gyrus) in an unanæsthetized, relaxed cat. Arrow indicates spikes on surface positive wave of the response. The magnitude of spontaneous variation in size of these responses is apparent.

If this spike corresponds to the first spike seen at the visual cortex to an incoming volley, it signifies activity within the afferent radiation (Bishop and O'Leary, 1938; Bremer and Stoupel, 1956). The spontaneous variation observed, in auditory evoked responses, is at least as great as that seen in the visual system.

The mouse, in a covered glass jar, was placed inside the cage with the cat. On the first few presentations of the mouse the cat showed similar excited behaviour to that described above. At this time, compared with the control value of $51 \pm 6{\cdot}0$ μV. the spike response was reduced significantly ($P < 0{\cdot}05$) to $31 \pm 5{\cdot}2$ μV., and the surface positive wave reduced ($P < 0{\cdot}001$) from the control amplitude of $80 \pm 3{\cdot}1$ μV. to $53 \pm 4{\cdot}9$ μV. The amplitude of the surface negative wave, $81 \pm 5{\cdot}6$ μV. was not significantly different from the control value of $76 \pm 2{\cdot}9$ μV. It seems probable that during these first few presentations of the mouse, the cat not only looked at it, but also listened—that is, searched the sensory field for auditory cues when the predominant stimuli were visual or olfactory. It may be recalled that similar behavioural conditions were obtained in one of the experiments when recording from the visual cortex. During the stage of early conditioning, the essential conditioned stimulus was the tone; yet the cat also looked round its box as if searching for some additional visual cue. In this case the cat was not looking at a *specific* visual stimulus (e.g. mouse or food, etc.) but appeared to be searching for one. The surface positive component of the primary wave was reduced in amplitude, but like the evoked response to click the surface negative response remained unchanged compared with the control value. The possibility therefore exists that the surface negative (late intracortical) wave is not depressed when a cat searches for some (unidentified) cue in the relevant sensory field, though the surface positive response is.

By the ninth presentation of the mouse, the general excitement which had characterized this cat's behaviour in the preceding trials was considerably reduced. Nevertheless the cat remained interested in the mouse, and sat watching it as it moved in the bottle. Indeed in the run to be described, the cat also bit the glass jar in what seemed a vain attempt to gain access. During this trial the surface positive wave of the evoked response to the click was significantly increased ($P < 0{\cdot}02$) to $90 \pm 3{\cdot}3$ μV. compared with the control response of $78 \pm 3{\cdot}5$ μV. The surface negative wave of $80 \pm 2{\cdot}8$ μV. was also increased significantly ($P < 0{\cdot}001$) over the resting value of $62 \pm 3{\cdot}2$ μV. The mean amplitude of the spike was increased from 40 ($\pm 4{\cdot}0$) μV. to 55 ($\pm 6{\cdot}8$) μV., though the difference was not quite significant ($0{\cdot}05 < P < 0{\cdot}1$).

From the cat's behaviour it is obvious when it is not searching the visual field, but it is much more difficult to decide when it is not searching the auditory field. It is possible, however, that in the experiment described

in the above paragraph the cat was no longer searching for any auditory cues and that in these circumstances the evoked responses to click were enhanced. Such a possibility would fit with similar results observed in comparable circumstances in the visual system (cf. late conditioning and negative orientational behaviour).

Discussion

There is one important difference, of considerable theoretical significance, between the results of experiments reported here and those of Hernández-Peón *et al.* (1957). The difference relates to the behavioural circumstances in which reduction in size of the photically evoked responses was elicited. Unless specific measures are taken to prevent a cat from *looking* toward the source of a non-visual stimulus, visual searching behaviour is likely to form part of the attentive response. It has been shown in this study that whenever such visual searching comprises part of the behavioural response, there is depression of the evoked potential to flash. Hernández-Peón *et al.* (1957) in describing the technique used in their experiments make no mention of any measures taken to prevent the cat looking toward the source of the olfactory or acoustic stimulus. Failure to take such measures would be sufficient to account for the apparent discrepancies between their results and those described here. A simple hypothesis which accounts for the results obtained by Hernández-Peón *et al.* (1957), and those described in the present paper, is that when a cat is called, or receives some other non-visual stimulus, evoked responses are attenuated *as a correlate of the search for visual information*, not because the visual information is irrelevant. It seems likely, therefore, that attenuation of an evoked response has an entirely different significance from that suggested by Hernández-Peón *et al.* (1956, 1957) and quoted in the Introduction.

The objection that the flash was a signal irrelevant to the perception of the mouse and hence "blocked" in the afferent pathway has been considered and rejected elsewhere (Horn and Blundell, 1959). Nevertheless, because this is clearly an important issue, it will be discussed in more detail. Since the mouse used in the present investigation was white, the retinal receptors which signal information about it will be the same as some of those which signal information about the flash. The duration of the response in the optic nerve to a flash of 1 m.sec. duration is of the order of 25 m.secs. (Hernández-Peón *et al.*, 1957). In so far as reduction of an evoked response is an index of a net change of sensitivity, the hypothesis that the cat "blocks" signals concerning the flash, but not those concerning the mouse would require that for some 25 m.secs. during the time the flash-evoked signals are being conducted, the sensitivity in the visual pathway is reduced, to be increased when the mouse, but not the flash, is present. In one cat flashes were delivered at half-second

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intervals so that fulfilment of this hypothesis would require that for about one-twentieth of the total time the mouse was present, information about the mouse would have to be rejected because information about the flash was being rejected. This conclusion could only be circumvented by making a number of highly improbable *ad hoc* assumptions about filtering devices of various sorts operating, on a temporal basis, at the retina. If the pathways conducting information about the flash and the mouse are common up to and including the area of cortex from which records were taken, sensitivity would then be reduced for at least 200 m.secs. (the approximate duration of the primary and secondary waves of the flash-evoked response)—that is, for almost 50 per cent of the time the mouse was present. Alternatively, it could be argued that when the mouse is present the retinal area signalling information about the mouse may remain fully sensitive, while the sensitivity of other retinal areas is reduced. This hypothesis is not particularly impressive since in that area whose sensitivity is unchanged, information about the flash would be signalled just as well as information about the mouse and hence there would be no "blocking" of the flash-elicited signals in these channels. Furthermore, if depression of the flash-elicited evoked response when the mouse is presented signifies selective blocking of the flash, what is signified when the flash response is unattenuated, before the mouse is presented? At this time the relaxed cat showed no behavioural evidence whatever of interest in the flash: so that if changes in an evoked response signify changes in perceptual gating (Bruner, 1958) we should have expected the presence of the mouse to have had no effect on the evoked response to flash. The fact that the mouse did have an effect weighs heavily against the view that the observed changes in the evoked potentials may be taken as indices of perceptual blocking.

There is also experimental evidence on human subjects against the view that sensory perception is limited by the selective exclusion of sensory messages at the periphery. Thus in experiments conducted by Broadbent (1954) each subject was given a pair of head-phones, each ear-piece being connected to a separate channel, and two lists of numbers were presented simultaneously. Thus one ear might receive 723 while the other simultaneously received 945. The listener was asked to reproduce all six digits in any order he chose. In the majority of those able to reproduce all digits the order of reproduction was either 723945 or 945723. That is, all the information from one channel appeared in the response before any of the information from the other channel. A mixed response of the type 792435 implying alternation of channels, was never obtained. Other control experiments confirmed that the results could not be accounted for on the supposition that the subject listened alternatively to each channel. Similar results were obtained using visual and auditory channels (Broadbent, 1956). Data from these simultaneous stimulation

experiments imply a short-term storage system for signals arriving from one of the channels. It is unlikely that such a storage system is situated at the sense organ.

The arguments that have been presented elsewhere (Horn and Blundell, 1959) and in the above paragraphs, render highly improbable the hypothesis that "blocking" of sensory messages at the periphery is an important mechanism whereby ". . . the span of conscious sensory perception . . ." is limited (Hernández-Peón *et al.*, 1957). Nevertheless, in spite of this disagreement on mechanisms, there is no reason to doubt that by some neural process irrelevant information is filtered out during attention to other relevant stimuli (cf. Broadbent, 1958).

Units in the visual cortex which respond to diffuse illumination also respond to movement of a discrete spot of light across the appropriate retinal field (Hubel, 1958). From studies of vision with controlled movement of the retinal image (Ditchburn, Fender and Mayne, 1959) this would be the predicted behaviour of units which transmit signals that allow for maintained perception of detail. A diffuse flash of light may therefore be a useful stimulus for activating cells which behave in this way and the evoked potential a useful index of their summated response. Changes in the evoked response would then provide some information about the summated responsiveness of these units to a photic stimulus. Decrease in amplitude of the primary wave and especially the surface positive component is likely therefore to be of some physiological significance. If, as has been found in the present study, this decrease is not accompanied by any increase in the duration of the wave, the amplitude change cannot be accounted for on the basis of the wider temporal dispersion of the component units.

The amplitude of the primary wave of an evoked response may be depressed as a result of (*a*) a reduced input to the cortex, (*b*) a changed responsiveness of the cortex to the thalamocortical volley or (*c*) both (*a*) and (*b*). The surface positive component of the wave probably represents early post synaptic activity in the cortex immediately dependent on the afferent radiation volley, while the surface negative wave signifies later intracortical activity (Bishop and O'Leary, 1938). It was found in experiments on both visual and auditory systems that the surface positive deflection may be reduced in amplitude while the surface negative deflection undergoes no significant change. Attenuation of the surface positive response is thus not necessarily due entirely to a changed responsiveness of the cortex to the afferent volley. In the auditory system, it was found that depression of the surface positive wave of the response to a click was associated with a reduction in the size of the spike attributable to activity in the afferent radiation. These considerations make it probable that depression of the surface positive component of the primary wave is due in part at least to a reduced thalamocortical input.

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Barlow (1952) has shown in human subjects that saccadic eye movements increase with attention to, and decrease when attention is withdrawn from, the visual field. Such saccadic eye movement may, in the photopic conditions of the present experiment result in a higher incidence of firing of retinal ganglion cells as the cat watched the freely moving mouse or searched the visual field, compared with when it did not do so. The signal would then be superimposed on a higher level of background activity and the amplitude of the response would be reduced. Even if saccadic eye movements are assumed to occur in cats, this explanation of the changes of the evoked response is unlikely to be complete. Inspection of Table I shows that the surface negative component of the primary response is not always significantly reduced when the surface positive wave is, and the surface negative wave may be increased when the surface positive deflection is unchanged. Hence the reduction of the surface negative wave when the cat watches the mouse cannot be attributed solely to a fall in the amplitude of the positive wave and may signify the operation of some other factor that modifies intracortical activity. Furthermore an explanation of this kind cannot account for changes in click-evoked responses in the auditory cortex. It seems possible, therefore, that an increase in saccadic eye movements with "attention" to the visual field may possibly account for some of the changes in evoked activity observed, but is unlikely to be the sole basis of those changes.

Whatever the mechanism which brings about attenuation of an evoked response, one of its effects might be, under certain circumstances, to improve contrast between stimulus and background activity. This would lead to loss of sensitivity in the system, but to an increase in specificity. It is conceivable that this mechanism would also tend to diminish the synaptic effectiveness of randomly occurring presynaptic activity without seriously interfering with the transmission of certain non-randomly occurring signals. In this way a clear path would be provided for a signal in the presence of a high level of neural noise. On the other hand it has been shown that when a cat ceases to "attend" to the sensory field of a given modality, evoked responses in that modality are not significantly depressed and tend, if anything, to be enhanced. Absence of an input-attenuating activity in a sensory channel would give a greater absolute sensitivity in that pathway. The animal could thus monitor its environment more sensitively, but less precisely.

Summary

(1) The electrical activity of the visual cortex of 6 unanæsthetized, freely-moving cats was studied by means of implanted monopolar electrodes. The evoked response to a flash of light was recorded when the animal was resting and when it was watching a mouse.

(2) The evoked response in the resting animal consists of a primary wave and a secondary wave, followed by a series of oscillations (tertiary waves) lasting at least 500 m.secs. from the completion of the secondary wave.

(3) When the cat watches the mouse the amplitude of all components of the evoked response and the amplitude of the waves of the background electrocorticogram are significantly reduced. The duration of the surface positive component of the primary wave is also reduced. It is considered unlikely that these changes in the primary and secondary waves of the evoked response are due to the pupillary constriction or to the motor activity which accompany the orientational response. Nor are they necessarily a consequence of the accompanying changes in the activity of the background electrocorticogram. It is, therefore, probable that mechanisms which bring about changes in the background electrocorticogram are different from those affecting the evoked potentials.

(4) The cats were then conditioned to receive a shock after a series of tones. It was found that the evoked response to flash was reduced when a series of tones was delivered, *only if there was some visual searching component in the cat's response to the acoustic stimuli.* If there was no visual searching in the behavioural response to the tones, the evoked response to flash was not attenuated.

(5) In one animal an electrode was placed on the auditory cortex and the response to click recorded in the relaxed, resting animal and compared with the response when the animal was watching a mouse. On the first few occasions that the mouse was presented, the amplitude of the click-evoked response was reduced. It is conceivable that at this stage the cat was searching for auditory cues associated with the mouse, that is, it was listening as well as watching. At a later stage, though the cat sat intently watching the mouse, the amplitude of the click-evoked response was increased. It is considered possible that at this time the cat was no longer searching for auditory cues related to the mouse.

(6) The findings are discussed and it is considered that attenuation of evoked responses might serve to improve sensory contrast between signal and background. The mechanism responsible for this attenuation may also serve to clear the path for a non-random signal in the presence of a high level of random neural noise. Absence of this input attenuating activity, e.g. in the visual system when behaviour is directed to an acoustic stimulus, could give a greater absolute sensitivity in that pathway. The animal would thus monitor its environment more sensitively though less precisely.

(7) The way in which the results differ from previous work is discussed and a possible explanation for these discrepancies advanced.

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THE EFFECT OF AUDITORY AND VISUAL STIMULATION ON THE SKIN POTENTIAL RESPONSE OF SCHIZOPHRENICS

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WORK on the reaction time of schizophrenics, Tizard and Venables (1957), Venables and Tizard (1956, 1958) and Venables and O'Connor (1959*a*), has shown the dependence of response on the parameters of the stimulus. The value of repeating this work on voluntary responses, in the field of involuntary response, lies in removing explanations of the behaviour from situations where attitudinal and "set" factors may be the preferred form of interpretation to one where more physiological constructs may be evoked. With this in mind the skin potential response has been adopted for study.

The aim of the experiment is twofold. Firstly, to provide evidence for the influence of non-specific background stimulation on the responses of active and withdrawn schizophrenics. It had been previously shown that the reaction time of active schizophrenics tended to be increased by the presence of background stimulation, and that of withdrawn schizophrenics decreased in similar circumstances. Secondly, to provide data on rates of adaptation of electrodermal response in different subjects so that a later experiment on the intensity of stimulation might be more economically planned.

Skin potential was adopted as a measure of involuntary response rather than skin resistance as it is electrically a less equivocal measure, it is less dependent on basal level (cf. Wilcott, 1958) and in so far as it may show two components in its waveform it has the possibility of providing more information than the equivalent resistive measure.

Consideration of other autonomic measures shows that either from their non-continuous nature (e.g. heart rate) or because of the difficulty of continuous measurement (e.g. blood pressure) or because of the lack of precision or difficulty of their measurement (e.g. vasodilation and constriction) they are inferior when precise measures of amount and speed of response are required.

Because, in the case of the schizophrenics, two diagnostic variables,

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activity-withdrawal, and presence and absence of paranoid symptoms (adopted because of the results of O'Connor, 1957, and Venables and O'Connor, 1959*a*) were to be examined in addition to the effects of the experimental variables of primary stimulus modality and presence or absence of background stimulation, a factorial analysis of variance design was adopted. This created the possibility of a more powerful and economical analysis of variables which in later studies could be examined singly.

Method

Apparatus

Skin potential was measured by means of two channel d.c. amplifier (Shackel *et al.*, 1958), whose relevant characteristics were: input impedance 1 megohm, drift less than ± 20 μV in 30 minutes, noise less than 10 μV peak to peak, non-linearity less than ± 3 per cent input signal, rise time to a step function input 100 msec. A backing-off circuit incorporated in the amplifier enabled standing skin potentials to be compensated so that recording of responses could take place about a null point.

The output of the d.c. amplifier was fed into an Evershed and Vignoles QU/RD 15 recorder. The paper speed used was half-inch per second, which made measurement of response times possible to better than 1/10th second. Electrodes were of the silver-silver-chloride type selected to have a standing potential of less than ± 100 μV measured in a 0·1 gramme per cent solution of potassium chloride. Their drift over a 20 minute period was less than 50 μV. They were constructed of 99·9 per cent pure silver discs 8 mm. in diameter, resin mounted in a rubber ring 15 mm. in diameter allowing a 1 mm. space for electrode jelly.

The electrode jelly was 0·1 gramme per cent potassium chloride solution with 2 per cent agar-agar. Potassium chloride was used as the electrolyte following the recommendation of Rein (1929). The amplifier was used in an unbalanced condition, a single earth electrode was placed over a portion of skin on the inner surface of the left upper forearm scarified to achieve a zero potential point. Two active electrodes were used, one just above the inner surface of the left wrist, the other on the palmar surface of the proximal phalanx of the left middle finger. The skin at each site was cleaned with ether before application of the electrodes. Scarification of the skin was carried out with fine sandpaper, a method which had been shown experimentally to produce results indistinguishable from more drastic methods of piercing or skin drilling and which was more suitable for use with psychiatric patients.

The noise level of the whole recording chain from electrodes to recorder was of the order of 20–25 μV peak to peak.

The auditory stimulus was a 90 db (re 0·0002 dyne per cm^2) 1,000 c.p.s. pure tone presented for one second through a loudspeaker situated 5 ft. in front of the subject.

The extraneous auditory background stimulus was 75 db white noise produced by the same loudspeaker, it was present throughout the whole of the session in which it was used.

The "quiet" background of the room in the absence of the above stimuli was found on measurement with a noise level meter to be approximately 40 db.

The visual stimulus was the illumination for one second of a milk white screen $1' 6'' \times 1'$ and situated 5 ft. from the subject at an intensity of 900 ft. lamberts or 99 db re 10^{-10} lambert (cf. Stevens, 1955).

The extraneous visual stimulus was the continuous illumination of the same screen at an intensity of 700 ft. lamberts or 95 db.

When the above two stimuli were not present the "dim" illumination reaching the subject's eyes by reflection from the screen was 0·95 ft. lambert or 69 db.

If a parallel between auditory and visual decibel scales can be considered following the suggestion of Stevens (1955) the visual stimuli are throughout more intense than the auditory.

In view of the possible effects of temperature on performance, the level in the experimental room was maintained as constant as possible. The mean temperature measured at the start of each session was 6·46 S.D. 3·4° F. The mean relative humidity over which no control could be exercised was 63·7 S.D. 8·1 per cent. All recording and presentation of stimuli were done in an adjoining room, the subject being left alone once the stimulus situation was set up.

Subjects

The psychiatric subjects were 32 male chronic schizophrenics of mean age 39·6 S.D. 9·0 years, who had been in hospital for a mean length of present admission of 8·6 years. The length of stay ranged from two to thirty-one years. They were divided on the basis of a rating scale (Venables and O'Connor, 1959*b*) into four groups on the basis of two orthogonal factors. These groups were: active—paranoid, active—non-paranoid, withdrawn—paranoid, and withdrawn—non-paranoid. Subjects in these four groupings were allocated at random to the experimental treatments.

The normal subjects were 16 members of the artisan staff of the same hospital. Their mean age was 46·9 S.D. 9·0 years, a figure which did not differ significantly from that of the schizophrenics. It is reasonable to assume that the normal subjects have a similar educational background and intelligence to that of the premorbid condition of the schizophrenics.

Procedure

The subject was seated in a comfortable easy chair and was reassured that he was not going to receive any shocks. The electrodes' sites were cleaned by rubbing briskly with ether and the forearm site scarified with

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sandpaper. Adhesive tape was placed in position to mark the chosen sites. Some latitude was allowed in position of wrist and forearm sites to avoid hair as far as possible. The electrodes were removed from the potassium chloride solution in which they were stored, excess moisture shaken off, electrode jelly applied to fill the space over the electrode and taped in contact with the skin. Standing potentials were measured and compensated for. Finally, the room lights were turned off, extraneous stimuli switched on if necessary, the subject finally reassured and the double thickness doors of the room closed.

Only one schizophrenic subject felt unable to take part in the experiment and had to be replaced. Twenty stimuli were given to each subject at approximately one-minute intervals. Some latitude in timing was desirable in order to present stimuli when no endogenous responses were present and to avoid any possibility of temporal conditioning. At the end of the series of stimuli the compensating potential was removed and the standing potential on the subject's skin again measured.

Experimental Design

The basic design was that of a four factor analysis of variance with two replications in the case of the schizophrenics and a two factor design with four replications in that of the normals.

The experimental factors common to normals and schizophrenics were: (1) Primary stimulus, Modality—Auditory or Visual. (2) Extraneous stimulation—Present or Absent. The two extra diagnostic factors in the case of the schizophrenics were: (3) Paranoid or Non-paranoid. (4) Active or Withdrawn. It should be noted that the extraneous stimulation where present was always in the "opposite" modality to the primary stimulus modality, thus for example the extraneous stimulus was visual when the primary stimulus was auditory and vice versa.

Results

Conditions at the Start of the Experiment

Preliminary analyses of variance showed that the schizophrenic groups allocated to the four factors under consideration did not differ significantly with respect to age, length of stay in hospital, or the temperature and humidity of the situation at the time at which they were tested. Similarly, subjects in the normal groups neither worked under significantly different conditions of temperature and humidity nor were of significantly different ages.

Basal level of palmar skin potential at the start of the experiment was independent of diagnosis within the schizophrenic group and did not differ significantly from that of the normal group. The mean level was $-8{\cdot}1$ mV.

Main Experimental Results

Although recordings were taken from the wrist electrode as well as that on the palmar surface of the middle finger they will not be considered here as their main use was as a control recording to establish that there were no changes in electrical conditions, and as a help in determining presence of movement artefacts in the palmar recording.

The main experimental results are considered under three main headings: (1) Numbers of responses, (2) Amplitudes of response, (3) Times of components of response.

(1) *Numbers of Responses*

(*a*) *Total number of responses given.*—Analysis of the schizophrenic data showed that a mean number of 10·3 responses were given by active schizophrenics, and 6·4 by withdrawn schizophrenics ($P < \cdot 05$). There was no significant difference in the number of responses given by paranoid or non-paranoid schizophrenics. The mean number of responses given in the absence of additional stimulation was 10·3 and in the presence of additional stimulation 6·4 ($P < \cdot 05$). The modality of the primary stimulus had no significant effect, nor was there any significant interaction term which might show a differential effect of additional stimuli of different modalities. That this effect of additional stimulation was found in schizophrenics as a whole was shown by the absence of any interaction term between the absence or presence of additional stimulation and either diagnostic variable.

In the case of the normals, no effect of either primary stimulus modality or additional stimulation was found. The mean number of responses was 10·8, practically identical with that observed in the schizophrenics under "quiet" and "dim" conditions.

(*b*) *Total number of responses before a break.*—Although many subjects gave a series of responses, missed several and then gave more to later stimuli, the number of responses before a break might strictly be considered as that which would be used to measure "true" adaptation. While there was no significant difference between the effects of either diagnostic factor, more responses were again given in the absence of additional stimulation, mean = 6·4, than with additional stimulation, mean = 2·7 ($P < \cdot 05$). In addition more responses, mean = 7·3, were given to auditory stimulation than to visual, mean = 1·8 ($P < \cdot 05$). There were no significant interaction terms to show differential effects of these variables with diagnostic grouping.

The normal group again showed no effect of primary or additional stimulation and gave a mean number of 6·6 responses close to that given optimally by schizophrenics.

(*c*) *Number of "late" responses* (*i.e. to stimuli* 6–20).—It was noted that after apparently adapting many schizophrenics gave subsequent

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responses. A point was taken from which these late responses were counted which could be considered as after the mean point of "adaptation" (4·5 responses) of the schizophrenic group as a whole. In view of the significance of the factor "activity-withdrawal" in the total number of responses but not in the number of responses before apparent adaptation we should expect that this factor was that which was responsible for later responses. This was found to be significantly so ($P < ·05$). Active schizophrenics gave a mean number of 7·1 "late" responses, while withdrawn schizophrenics gave a mean of 4·0. The mean number for normals who showed no effect of type of stimulation was 6·8, again comparable with the optimal figure for the schizophrenics.

(*d*) *Biphasic responses.*—Responses have been counted as such up to this point without reference to their waveform. Among the schizophrenics 28·1 per cent showed biphasic responses at some time during their experimental session, while these responses were shown by 62·8 per cent of normals. This difference was significant ($P < ·05$). There was no significant differential effect of diagnostic or experimental grouping in schizophrenics or normals upon this variable.

Biphasic responses were defined as such only when there was a negative and a subsequent positive deflection present, although in some cases

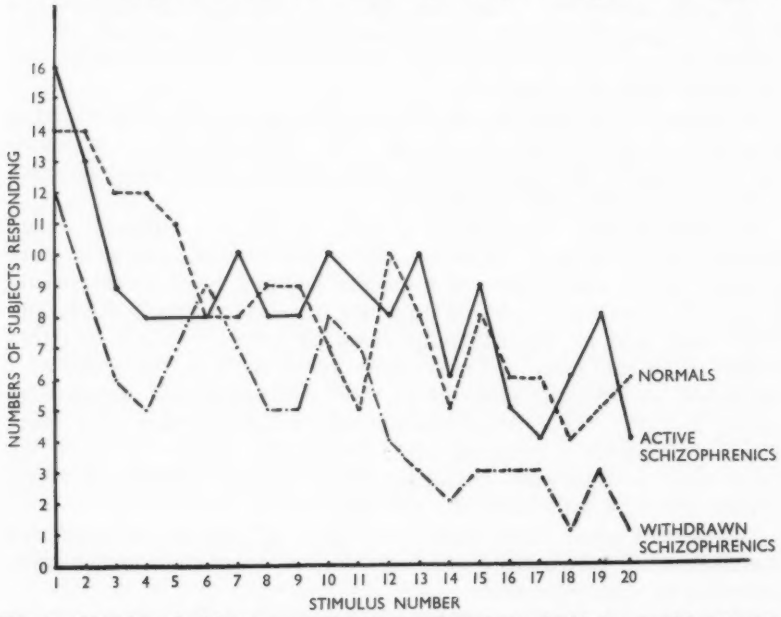

FIG. 1.—Number of subjects responding in normal, active and withdrawn schizophrenic groups.

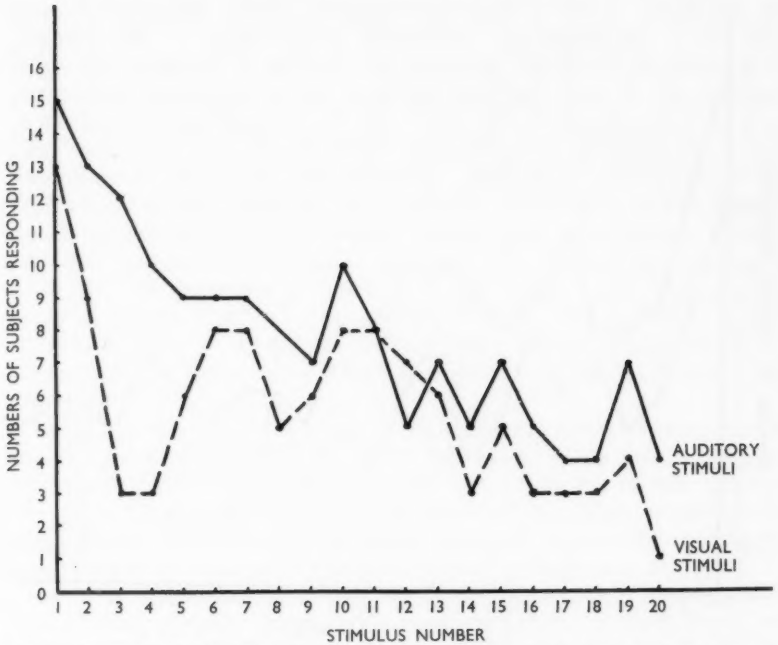

FIG. 2.—Number of schizophrenic subjects responding to auditory and visual stimuli.

there was a negative and then subsequent positively tending response which nevertheless did not extend in a positive direction beyond the level at the start of the initial negative deflection, which was taken as zero.

Figs. 1, 2 and 3 show the number of subjects giving responses to each successive stimulus grouped respectively by the factors activity-withdrawal, modality of primary stimulation, and absence and presence of additional stimulation. The number of normal subjects giving responses to each stimulus are also shown. These figures show in graphic form the findings of the statistical analyses.

In fig. 1 it is seen that practically without exception the active schizophrenics give more responses than the withdrawn throughout, but that the differential effect of this factor is shown later in the series more than in the early stages. Fig. 2 shows the greater rate of adaptation to visual stimulation than to auditory with subsequent recrudescence of response to visual stimulation to a degree not dissimilar from that in response to auditory stimulation. Finally, fig. 3 shows the general higher level of response in absence of additional stimulation compared to that when additional response was present.

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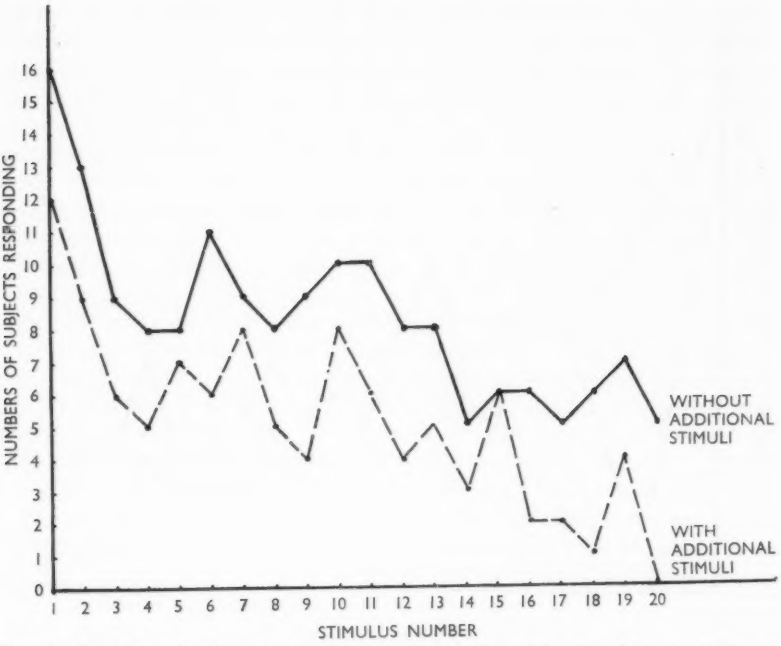

FIG. 3.—Number of schizophrenic subjects responding with and without additional stimulation.

(2) *Amplitude of Response*

The amplitude of each response was measured from the level at which the deflection was first detectable. In general this was the same level at which stimulation took place, but in the few cases where there was some continuous general change in the standing potential throughout the experimental session the point used for measurement gave a more realistic measure of response amplitude than otherwise.

All but two schizophrenics and one of the normal subjects gave an initial negative response either as the sole component of a uniphasic waveform or the first component of a biphasic waveform. For the three aberrant subjects the amplitude of their uniphasic positive responses was used as a figure for response amplitude.

Two possibilities are available to give a variable for analysis, either (*a*) the mean amplitude of those responses which were made, or (*b*) the mean amplitude of those responses which might have been made, i.e. 20; in other words a figure representing the total potential output per twenty stimuli. Both these variables were analysed.

(*a*) *Mean amplitude of responses made.*—Analyses of the schizophrenic

data showed that active schizophrenics gave a mean amplitude of response of — ·64 mV and withdrawn schizophrenics — ·43 mV. A greater response, — ·64 mV, was given to stimuli in the absence of extraneous stimulation of the opposite modality than in the presence of additional stimulation, — ·43 mV. However, a significant interaction term between two factors indicated that the effect of additional stimulation was solely on the active schizophrenics. Withdrawn schizophrenics in both situations gave responses of — ·43 mV, while active schizophrenics gave a response to a primary stimulus alone of mean amplitude — ·84 mV and with additional stimulation of — ·44 mV. Both main effect and interaction are significant at the ·05 level. In addition greater responses, mean amplitude — ·67 mV were given to auditory stimuli than to visual, mean amplitude — ·39 mV ($P < ·01$). There was no significant interaction term to show any differential effect of modality of additional stimulation.

In the normal group no effects of experimental variables were shown and the mean response amplitude for this whole group was — ·23 mV. This figure is surprisingly low, however in view of the greater number of biphasic responses given by the normals it is possibly explicable in terms of the attenuation of the initial negative response by the superimposition of the subsequent positive phase (cf. Wilcott *et al.*, 1957).

(*b*) *Mean amplitude per twenty stimuli.*—Analysis of the schizophrenic data on this variable repeats with more clarity the position found in relation to the variable "mean amplitude of responses made." A significant ($P < ·01$) interaction term shows that active schizophrenics in the absence of additional stimulation give a mean response amplitude over 20 stimuli of — ·66 mV, while in the presence of additional stimulation this figure falls to — ·17 mV. No effect is observed with withdrawn schizophrenics where the mean amplitudes are — ·17 and — ·18 mV respectively. In the case of normals the mean group response is — ·18 mV, no effects of experimental variables being evident.

These results are shown in graphic form in fig. 4, where the mean amplitude of response for each of the twenty stimuli are plotted. First are the data for the active schizophrenics in the condition with no extraneous stimulation, secondly are plotted the combined data for the active schizophrenics with extraneous stimulation and for the withdrawn schizophrenics in both conditions, shown not to differ in the foregoing analyses, and thirdly data for the whole of the normal group.

The greater responsiveneses of the active group in "quiet" and "dim" conditions is clearly seen, also the apparent lack of adaptation of the normal group although at a low level of response. Without explanation at the present moment is the regular phasic nature of the level of response shown most markedly in the active schizophrenic group without additional stimulation, but also to a lesser degree in the other schizophrenic groups.

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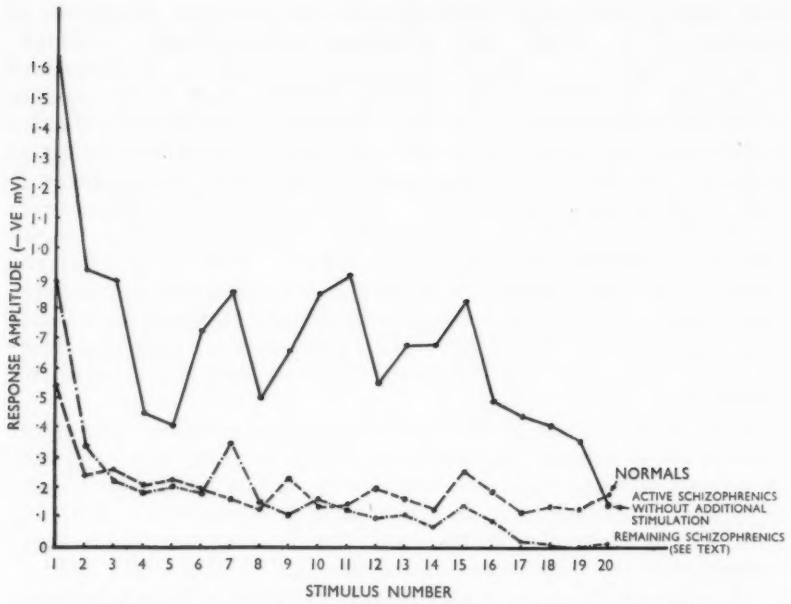

FIG. 4.—Amplitude of negative responses given by normals and active schizophrenics without additional stimulation; active and withdrawn schizophrenics with additional stimulation, and withdrawn schizophrenics without additional stimulation combined.

A suggestion of a phasic pattern is just apparent in the normal group although with a different periodic rate.

Fig. 5 shows the mean amplitude per response separately for auditory and visual primary stimuli. Here as with the data for numbers of responses (cf. fig. 2) the greatest difference between modalities is shown early in the session.

(3) *Times of Components of Response*

Two temporal measures are subject to analysis: (*a*) the latency of response, i.e. the time between the start of the presentation of the stimulus and the point of inflexion of the record at the commencement of the response, (*b*) the time of the response to reach its peak negative amplitude from the above point of inflexion.

Also measured was the time to reach the peak positive amplitude in the case of subjects producing biphasic waveforms. In view of the incompleteness of the data on this variable it will not be analysed except to mention that the peak positive amplitude was reached on average 6·3 seconds after the point of peak negative deflexion in the schizophrenics and 5·0 seconds in the case of the normals.

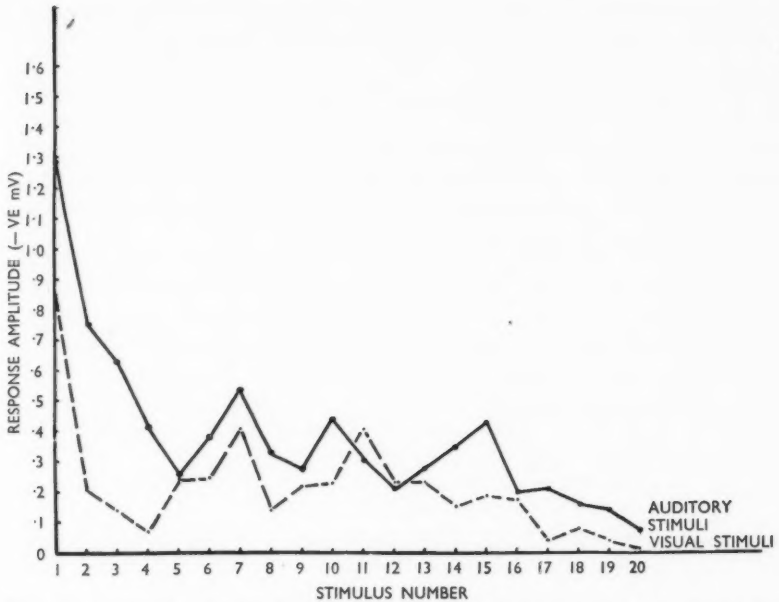

FIG. 5.—Amplitude of negative responses given by schizophrenics to auditory and visual stimulation.

(*a*) *Latency of response*.—Analyses of variance carried out on the schizophrenic data yielded a significant ($P < \cdot 05$) interaction term between the factors activity—withdrawal, and presence and absence of additional stimulation. No other interactions or main effects were significant. This interaction term indicated a differential effect of additional stimulation on active and withdrawn schizophrenics. The mean latency of the active schizophrenics without additional stimulation was 1·8 seconds, and with additional stimulation 2·1 seconds. In the case of the withdrawn schizophrenics the reverse is the case; with additional stimulation the latency is 1·8 seconds, without 2·4 seconds.

In the normals, analysis showed none of these effects, the mean latency of 2·0 seconds comparing exactly with the overall mean latency of the schizophrenics of 2·0 seconds.

(*b*) *Time to peak negative amplitude*.—Four interaction terms all significant at the ·05 level resulted from the analysis of the schizophrenic data. These indicated that active-paranoid schizophrenics were faster than the rest with a time of 2·0 seconds; for active non-paranoids the time was 2·9 seconds, withdrawn paranoids 2·7 seconds and withdrawn non-paranoids 2·6 seconds. This comparison just failed to reach

significance in the case of the latency data, where the active paranoids had a figure for latency some three-quarters of that of the other three groups.

The effect of additional stimulation in active and withdrawn groups is parallel to that shown on the latency data. Active schizophrenics without additional stimulation take 2·3 seconds to reach peak amplitude, while in the presence of additional stimulation they take 2·7 seconds. In the withdrawn schizophrenics this figure is 2·3 seconds with additional stimulation and 3·0 seconds without.

The other two interaction terms are concerned with the effects of auditory and visual stimuli in the two diagnostic subgroups. Their interpretation is somewhat equivocal, but it will be shown in the discussion that a useful explanation of the findings can be made with reference to other experiments.

No effect of experimental variables was seen in the normal group, where the mean time to peak amplitude was 2·3 seconds compared with 2·6 seconds for the schizophrenic group as a whole.

Summary of Results

Before going on to discuss these results it is necessary to summarize the main findings. A consistent theme running through them all is the effect of presence or absence of additional stimulation on the responses of schizophrenics rated as active or withdrawn.

The essential features of the findings on this point are summarized in Table I.

Table I.—Summary of Data Showing Effect of Additional Stimulation on Active and Withdrawn Schizophrenics

Group	*Additional stimulus*	*Latency*	*Mean voltage per response*	*Time to reach peak response*	*Mean number of responses*
Unit		*sec.*	*MV*	*sec.*	
Active	Absent	1·8	·84	2·3	13
	Present	2·1	·44	2·7	7
Withdrawn	Absent	2·4	·43	3·0	7
	Present	1·8	·44	2·3	6

Here it is seen that active schizophrenics in a "dim" and "quiet" situation produce more responses, of greater voltage, in a shorter time and after a shorter latency than similar subjects in "bright" or "noisy" conditions. In converse withdrawn schizophrenics produce roughly the same number of responses, and of the same voltage, but more quickly and after a shorter latency in "bright" or "noisy" conditions than in "dim" and "quiet" conditions. In other words, additional stimulation only affects the *speed* of response of withdrawn subjects while it affects both speed and amount of response in active subjects.

Secondly, consistency is shown in the effect of auditory and visual primary stimulation. Although there is an overall greater amount of response (— ·67 mV) to auditory than to visual stimulation (— ·39 mV) reference to fig. 5 indicates that this is mainly due to a large difference in the responses to the first four stimuli. The mean level of response for these four stimuli are — ·77 mV for auditory and — ·32 mV for visual stimuli ($P < ·01$). Similarly it is only in the early responses, before a break, that the factor of primary stimulus modality has a significant effect where 7·3 responses are given to auditory and 1·8 to visual stimuli. This may be seen clearly in fig. 2. The effect of modality of stimulus is apparently therefore only to be seen early in the experimental session.

Another finding is the general greater speed of response of the active-paranoid schizophrenics; this is shown in Table II.

TABLE II.—TEMPORAL DATA SHOWING DIFFERENCES BETWEEN SCHIZOPHRENIC SUB-GROUPS

Group	*Unit*	*Latency** *sec.*	*Time to reach peak response* *sec.*	*Mean of† auditory —visual RT* *sec.*
Active-paranoid	..	1·7	2·0	·41
Active-nonparanoid	..	2·2	2·9	·66
Withdrawn-paranoid	..	2·1	2·7	·64
Withdrawn-nonparanoid		2·0	2·6	·60

*Just not significant but included for completeness.
†From Venables and O'Connor (1959).

Although not quite significant the data for latency are given as well as the time to reach peak amplitude of response. Also included for comparison are reaction time data from Venables and O'Connor (1959*a*) on diagnostically similar but not the same group of patients.

DISCUSSION

The finding of greater responsiveness of active schizophrenics in a minimally stimulating situation and greater speed of withdrawn schizophrenics in a situation where the primary stimulus was presented against a background of additional stimulus is a confirmation of results obtained in the field of reaction time (Tizard and Venables, 1957). An important additional finding is, however, that whereas speed of response appears to be affected in both groups, it is only in the active schizophrenics that the factor of background stimulation has influence on the size and number of responses made. This points to the possible influence of two mechanisms in determining the responses of active schizophrenics while only one is operative in the performance of the withdrawn schizophrenics. In a recent review Samuels (1959), hints at the possibility of

different effects of elements grouped together under the heading of reticular formation. She points out that studies indicate that while it is possible that the diffusely projecting thalamic section may in part influence the timing of cortical functions the general function of the brain-stem section is more clearly that of control of "arousal." It is far too easy to interpret results in terms of the indefinite possibilities of influence of the reticular formation, but this distinction between influence on speed alone as well as on total amount of response may well be useful and productive of further distinction in the course of experimentation.

The dual function of additional "non-specific" sensory stimulation in increasing the response of one diagnostic group and decreasing that of another suggests that something akin to the inverted U-shaped function of arousal (Hebb, 1955; Schlosberg, 1954) may be operative. In the case of normals it can be hypothesized that the optimal level of arousal (Hebb's non-specific cortical bombardment) is broad, and as indicated by the results of the present experiment, changes in background stimulation of the amount used do not bring about a significant change in response. However, it is hypothetically possible that neither active nor withdrawn schizophrenics are operating in day to day conditions at optimal efficiency. In the case of withdrawn schizophrenics the addition of non-specific stimulation increases the level of arousal from a sub-optimal to a more nearly optimal condition. In the case of the active schizophrenics the decrease in sensory input reduces arousal from a supra-optimal condition to one where response is more efficient.

An interesting point is the distinction between the function of the sensory input as a cue, a stimulus to which response is to be made, and sensory input as a non-specific arousal function. As work reviewed by Samuels points out, this distinction is probably a function of the timing of the stimuli. In this experiment the primary stimulus was only present for one second every minute and the more important stimulus for arousal may therefore be the continuously present state of background stimulation. Given "cue" stimuli closer together in time their nature may determine the arousal function. Sharpless and Jasper (1956) give a time of 10–15 seconds as a figure for which the "phasic" habituation resistant form of the arousal reaction is active after a single stimulus. Possible confirmation of this is the work on the "paradoxical effect" in reaction time (Venables and Tizard, 1956, 1958), where it is shown that when a visual stimulus was presented once every eight seconds and was intense it brought about an increase in reaction time. It is unfortunate that in this experiment no distinction was made between active and withdrawn schizophrenics. However, as this phenomenon was shown only on the first occasion of testing, the anxiety of being in an unknown situation may have led to the arousal of both groups in the presence of

intense stimulation which was supra-optimal, this gives a possible explanation of the results.

Important also is the modality of the non-specific sensory stimulation. Bernhaut, Gellhorn and Rasmussen (1953) showed "sensory stimuli listed in decreasing order of ability to produce an arousal reaction are: (i) nocioceptive, (ii) proprioceptive, (iii) auditory, and (iv) optic." Why then in the present experiment is there no effect of modality of additional background stimulation shown? Two explanations are possible. One, given an equality of decibel scales for light and sound (Stevens, 1955), the intensity of visual background (95db) was greater than that of auditory background (75db). Two, a reaction time study, Venables and O'Connor (1959*a*), had shown that with most schizophrenics RTs to visual stimuli were faster than those for auditory at intensities which gave the opposite relations for normals. It is thus possible that the additional intensity of, and reactivity of schizophrenics to, the visual stimuli used resulted in an effect indistinguishable from that given by the auditory stimulus.

This last study showed that active paranoid schizophrenics in contrast to the other groups gave responses which were on average faster to auditory than to visual stimuli. We might therefore expect to find somewhere in the present data indication of a greater reactivity to auditory background in this group of subjects in comparison to the other groups. The variable "time to reach peak response," on analysis, yielded two interaction terms the interpretation of which was not clear. However, detailed examination of the data shows the results given in Table III. Here it is seen that in the active group the preponderant deleterious effect of additional stimulation is in the auditory modality and in the active paranoid group, giving confirmation of the above suggestion.

TABLE III.—EFFECT OF VISUAL AND AUDITORY ADDITIONAL STIMULATION ON SCHIZOPHRENIC SUB-GROUPS

	Change in time (sec.) to reach peak response due to additional stimulus	
Group	*Visual*	*Auditory*
Active paranoid ..	+0·1	+1·5
Active non-paranoid ..	+0·2	−0·3
Withdrawn paranoid ..	−0·6	−1·0
Withdrawn non-paranoid	−0·6	−0·7

Also confirming the results of the RT study first mentioned are the results given in Table II, where the data show an overall greater speed in the active paranoid group in comparison to the other groups. It is perhaps worthy of note that the slight differences in RT in the remaining groups are preserved in the skin potential data.

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SUMMARY

The skin potential responses of a group of 32 schizophrenics and 16 normals were measured. The schizophrenics were divided on the basis of ratings of presence or absence of paranoid symptoms and of social withdrawal or activity. Auditory or visual stimuli were used either in the absence or presence of additional stimuli of the "opposite" modality. Confirmation of previous reaction time results was achieved by the finding of greater responsiveness of active schizophrenics in minimally stimulating conditions while greater speed of response was shown by withdrawn schizophrenics in the presence of additional stimulation. Also in confirmation of previous results was the greater speed of active paranoid schizophrenics in contrast to the other diagnostic groups. The results are discussed in relation to hypothesized arousal mechanisms.

This work was carried out at Springfield Hospital, London, by the kind permission of the Medical Superintendent, Dr. H. C. Beccle. Thanks are due to Mr. B. Shackel who made available the circuit of the d.c. amplifier prior to publication, and to Mr. E. Sayer who constructed the apparatus and developed the electrodes.

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THE SOMATIC SENSE OF SPACE (CHORÆSTHESIA) AND ITS THRESHOLD

BY

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> The notion of extension is so familiar to us from infancy, and so constantly obtruded by everything we see and feel, that we are apt to think it obvious how it comes into the mind; but upon a narrower examination we shall find it utterly inexplicable. It is true we have feelings of touch which every moment present extension to the mind; but how they come to do so, is the question.
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>
> The sensations of touch are so connected, by our constitution, with the notions of extension, figure and motion, that philosophers have mistaken one for the other, and never have been able to discern that they were not only distinct things, but altogether unlike.
>
> THOMAS REID (An Inquiry into the Human Mind on the Principles of Common Sense, 1764).

INTRODUCTION

THE ability to perceive the shape of objects held in the hand is generally explained by a synthesis of touch and kinæsthesis. This implies that either the spatial aspects of objects cannot be perceived on the basis of skin sense alone or that a dermal spatial sense plays a secondary role to kinæsthesis. The experiments which will be described are an attempt to establish the existence, the threshold and the importance of a dermal space sense. This sense we propose to combine with kinæsthesis (joint, ligament and muscle sense) to form what we will call the Somatic Sense of Space and for the sake of brevity we will name this sense Choræsthesia (Greek, chora—place or country).

Two-point discrimination and the sense of passive joint movement are frequently lost together with central nervous lesions and it may be that any dissociated loss of these two senses which can be discovered is a reflection of the crudity of the method of testing joint sense. The correspondence between two-point discrimination and joint sense does not seem to have aroused much curiosity on the part of physiologists and neurologists although the fact that two apparently different senses can

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be lost with lesions of the same nervous pathway, the posterior columns, is, on the face of it, a little odd.

On the basis that function correlates with anatomy it can be argued that in testing two-point discrimination and joint sense the same function is being tested. The only similarity we can see between the two tests is a spatial one. Should joint sense be tested by measuring the smallest movement the subject can detect, then the similarity between this test and the test of two-point discrimination can be described as the measuring of the threshold of space. Consequently we think it justifiable to speak of a Somatic Sense of Space. To apply the term Sense of Space to two-point discrimination is not original for reference was made to it by Head and Thompson (1920*a*) who, without naming the originator, said that it was proposed in 1858.

We anticipate that an objection will be raised to the Sense of Space on the ground that an awareness of two points touching the skin allows the inference of space between them, that is to say, space is not felt but inferred. However, since no one will deny that he can feel (whether or not he uses the term feel or some other is irrelevant here) the round shape of a penny pressed on the palm, we must suppose that it is not the sense of resistant or occupied space that is to be rejected but the sense of non-resistant or unoccupied space. Whether or not the sense of non-resistant space is valid as a sense can perhaps be decided by reference to vision.

Should a man look down a deep hole in the ground his statement that he can see the hole could be countered by the suggestion that, since his retinal receptors are not stimulated, he does not really see the hole but only the ground round it, that is, he is permitted to say he sees light space but not dark space. The man may reply that, if he is in a completely darkened room, it would be wrong for him to say that he sees nothing for he is quite aware that he sees a dark expanse. However the objection could be sustained that, if his optic nerves were severed, he would continue to be aware of the dark expanse, and that the verb *to see* would be inappropriate since his visual apparatus was no longer functioning. If this objection is valid, and we think it is, it follows that the dark expanse is an image or phantom analogous to a phantom limb; more accurately it is analogous to the feeling a man has when, holding his arm up in the air and without touching it, he says that he "feels" his arm, for we imagine that what he feels is not different from a phantom limb. It is improbable, too, that a man born blind, when placed in a darkened room, would claim that he is aware of a dark expanse and it follows that the dark space image is evolved over a period of seeing light space. Again this is analogous to a phantom limb for a child born without a limb will not have a phantom for that limb. We believe therefore that dark space is an image constructed from light space and that the latter is prior to the

former. A picturesque analogy would be a painter, who having unlimited paint but no canvas, used his paint as clay to mould a board which, when hardened, could be used as a surface upon which to paint. The more pictures he painted on the board the more solid it would become.

If our supposition is correct that dark space is an image capable of persistence despite the failure of the peripheral visual apparatus, then we admit that in the usage of words in physiology, as distinct from psychology, it is incorrect to say that dark space is seen. Nevertheless, we prefer the usage of the lay public and maintain that dark space is visible.

It was Kant's view that space is a representation *a priori*. His distinction between space on the one hand and light, for example, on the other, whatever validity it may have in philosophy, has doubtful relevance to physiology. Sight is not affected by light, as he remarked. Sight *is* light and the problem of the origin of spatial consciousness is equally applicable to light consciousness. Thus it could be claimed that light and all other sensations are *a priori* for they are neither the causes nor the products of experience but, on the contrary, constitute experience itself. But the statement that space and light are *a priori* experiences on the ground that they are not posterior to some other experience does not mean that they do not have a causal relationship to neuronal activity. The truth is that with regard to experience, metaphysics and empirical science, like water and oil, do not mix. The confusion introduced by Kant originated, partly at least, in his using the term *a priori* in connexion with space for it is strictly applicable only to knowledge and not to experience.

Reference has been made to Kant since his views on space, according to William James (1907), generated a great deal of controversy among psychologists and physiologists at the end of last century. Whether the relative merits of the so-called sensational and supra-sensational schools still exercise the minds of physiologists and neurologists is difficult to judge. Certainly a perusal of the literature leaves the impression that space, in some mystical way, is considered to be stuck on to the sensations of light and touch, and this impression engenders the belief that physiologists and neurologists, knowingly or unknowingly, belong to the supra-sensational school. Walshe (1942), for example, in his criticism of Head reveals himself to be, by intention, a thorough-going Realist; yet his contentment with four dermal sensory modes, touch, pain, warmth and cold, betrays a Kantian point of view. His injunction not to confuse thoughts with things is impossible to follow since the discrimination of the two points of a two-pointed object, which amounts to an awareness of its spatial aspects, is stated by him to be a judgment. The object is thus to be considered real but its space only a mental phenomenon, a philosophy which, although commonly held, is an unconvincing mixture of Realism and Idealism.

The conflict between the two schools, like most other verbal conflicts,

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arises no doubt in the use of language. We therefore feel obliged to offer a definition of sensation in the following terms. Experience is sensational when it can be prevented by lesions of the peripheral sensory receptors. In the case of vision the evidence is that light space is dependent on the retina and consequently, since dark space is derived from light space, all visual space is, in our meaning of the word, sensational.

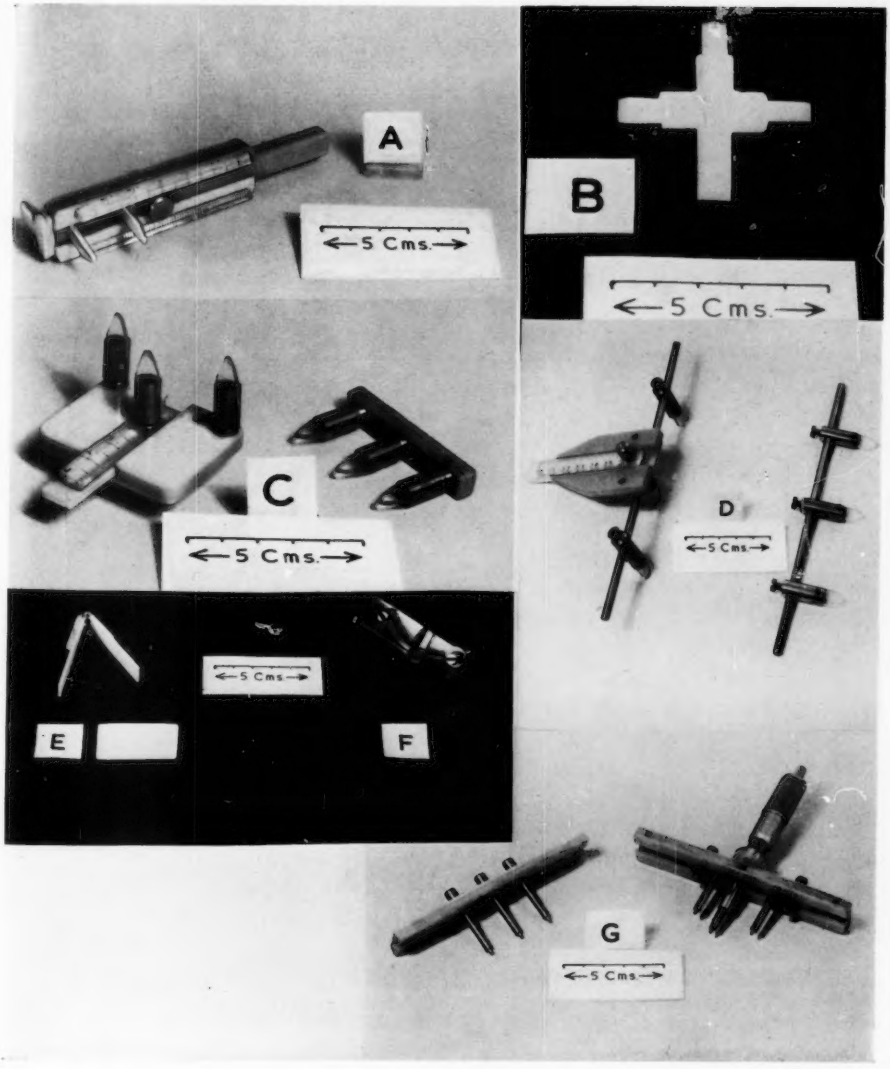
Returning to touch we hope that the above digression will make our point of view clear. We submit that there is a non-resistant space image constructed from resistant space feelings. We accept that a Dermal Sense of Space should be, strictly speaking, synonymous with a Dermal Sense of Resistant Space but, as we have indicated above in the case of vision, we prefer the usage of words which permits a man to "feel" the space between the two points of a compass.

In our experiments we have worked on the basis that a dermal touch feeling and a dermal space feeling are two different feelings. Our justification for this is based on introspection, for a penny pressed on the hand feels both hard and round. To disagree with this is to deny common sense.

METHODS

Introduction.—For the purpose of our investigation we considered space in terms of two planes called Surface Space and Depth Space, the former being parallel to the skin surface and the latter perpendicular to it. Several instruments were devised for tests in each plane and these required the subject to discriminate between a test-object and a control-object, the only difference between them being spatial. The spatial difference was variable and measurable. Every test was begun with a difference that was easily appreciated and this difference was gradually reduced until it could no longer be appreciated. The test-objects were pressed firmly on the skin in the appropriate sites on the subject's dominant hand, and kept in contact until he identified them, rightly or wrongly, or stated that he was unable to hazard a guess. The objects were not moved across the surface of the skin so that the thresholds measured can be described as thresholds of *static* space as distinct from *kinetic* space.

The sites used were: (1) the mid-point of the tip of the index finger, (2) the palmar surface of the proximal phalanx of the index finger, (3) the middle of the palm towards the ulnar side, and (4) over the first dorsal interosseus muscle. The tests for surface space were begun with the following differences for the sites stated: finger-tip 3 mm., first phalanx 7 mm., palm 12 mm., dorsum 18 mm., and for all sites the spatial difference was reduced by 1 mm. at a time. For depth space the initial spatial differences and decrements were as follows: finger-tip 1·25 mm. with decrements of 0·25 mm., first phalanx 3·0 mm. with decrements of 0·50 mm., and palm 3·75 mm. with decrements of 0·63 mm.



TEST OBJECTS.

To illustrate article by S. Renfrew and I. D. Melville.

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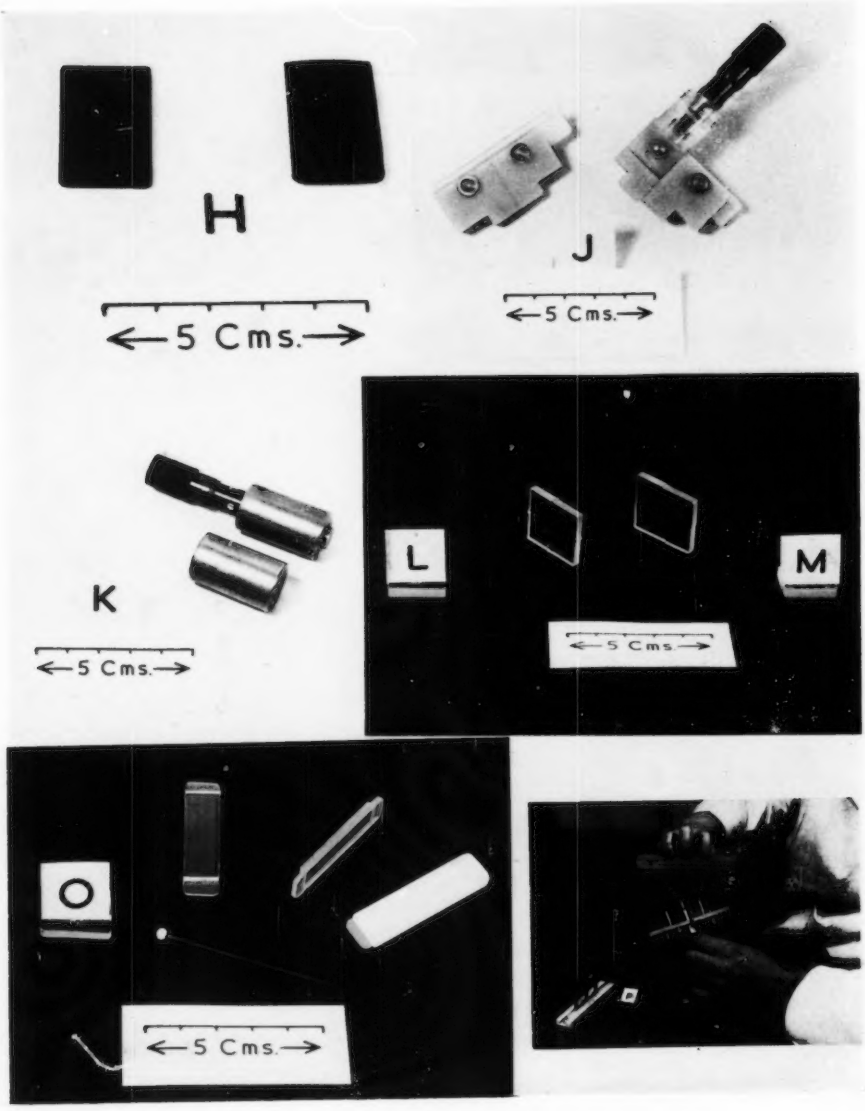

TEST OBJECTS.

To illustrate article by S. Renfrew and I. D. Melville.

Subjects.—The tests were made on thirty young house-physicians who were not examined if they had lost sleep the previous night, since it is known that fatigue impairs performance in sensory tests. The subject sat in a comfortable chair, his eyes closed, and the hand under test supinated and resting on his knee.

Scoring.—In an experiment, twenty tests were made for every measured difference between the test-object and its control. The twenty tests consisted of the application of the test-object ten times and the control-object ten times, in a random manner. Their application was dictated by the fall of twenty marked cards which were shuffled and dealt. The subject passed a test if in identifying the objects he made two mistakes or less out of the twenty applications, that is, scored eighteen or more. Testing was continued until the subject made more than three mistakes, or made three mistakes in each of two successive tests, and when this happened the preceding test difference was taken as the threshold. A few examples will illustrate the scoring system.

	Spatial difference in mm./score				
Finger-tip	3/20	2/19	1/16		threshold 2 mm.
First phalanx	7/20	6/17	5/18	4/16	threshold 5 mm.
Palm	12/20	11/20	10/17	9/17	threshold 11 mm.

The figures in the tables are thresholds arrived at in this way. About 60 to 100 applications of the test-objects were required to reach a threshold value in a single test.

Test-objects.—The objects used in the experiments are shown in the Plates (*facing* page 98) and described below. They are made so that as far as possible the parts which come into contact with the skin are of acrylic, a poor heat conductor. In the design, manufacture and use of some of the objects, the Imperial system of measurements was used because of engineering requirements, but all the results are shown in the Metric system. This explains the rather odd numbers which appear.

Test-objects and Procedures for Surface Space

Two-point object (A in Plate XIX).—This was used in the test for two-point discrimination. The "one-point" consists of two blades 0·5 mm. apart, in order to minimize sharp and blunt feelings which the subject could use to assist discrimination.

Direction objects (B).—These are blades with knife edges of various lengths, ranging from 1 mm. to 12 mm. at intervals of 1 mm. The subject was asked to identify the *direction* of a blade placed either across or in the long axis of the hand. There is no control object in this test, the discrimination being of the change of direction of the blade.

Size objects (B).—The same blades were used in a test to find the smallest *size* of blade which the subject could distinguish from control-objects.

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The control on the finger-tip was a wire 0·5 mm. diameter, and on the first phalanx and palm was a blade 1 mm. long. In this test the objects were applied across the long axis of the hand.

Shape objects (C and D).—These consist of three blade-points, the middle one of which can be moved out of line by a measured distance. Thus the amplitude or height of the triangle formed by the three blade-points is variable. The blade-points of the control-object are in a straight line. The outermost blade-points of these objects, which form the base of the triangle, can be separated by measured distances when required.

For tests on the finger-tip and first phalanx the base of the triangle was 2 cm., and on the palm 4 cm.

Hinge object (E).—This is a simple hinge, the control-object being a single blade. The hinge was applied to the palm only, with the ends of the blades separated by a measured distance.

Curved object (F).—This is a celluloid strip bent into an arc, the amount of bending being measurable on a scale. The control-object is a straight strip of similar size. Testing with these objects was also confined to the palm.

Test-objects and Procedures for Depth Space

Micrometer-peg objects (G).—These consist of three brass pegs with rounded tips of 1 mm. diameter, the middle one of which is attached to a micrometer so that it can be protruded by measured distances. The control-object has three similar pegs in a straight line. The objects were applied perpendicularly to the skin (*see* fig. 1). For tests on the finger-tip, first phalanx and palm, the pegs were separated by 1 cm., 1·5 cm. and 2 cm. respectively.

Curved blade objects (H).—These consist of pieces of acrylic 1·9 cm. long and 0·16 cm. thick, with one end in the shape of an arc. The depth of the arc is measured as fig. 2 shows. The end of the control-object is flat. Tests with these objects were confined to the finger-tip.

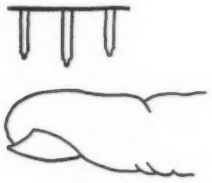


FIG. 1.

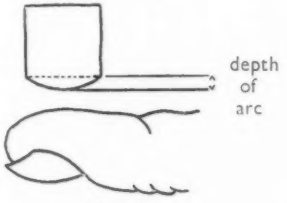


FIG. 2.

Micrometer-blade objects (J).—The test-object consists of a micrometer attached to one of a pair of acrylic blades so that a step of variable depth can be formed. The control-object is a pair of similar blades milled so

that the surface to be applied to the skin is flat. Each blade is 1 cm. long and the blades of both the test-object and the control-object can be separated by a measured distance when required. Blades of the following thicknesses were used in the tests: 0·08, 0·16, 0·32, 0·64 and 1·27 cm. The tests were confined to the finger-tips and fig. 3 shows the mode of application.

With this test-object, testing with a step of under 0·13 mm. becomes inaccurate for mechanical reasons, and because of this the next object was designed.

Cylinder-peg object (K).—This is a hollow brass cylinder of diameter 2·54 cm. A brass peg, concentric with the cylinder, and attached to a micrometer, is fitted closely inside the cylinder so that it can be protruded by a measured distance. The circumference of the brass peg or core is 2·54 cm. The control-object is a solid cylinder with a flat end. This test was also confined to the finger-tip and fig. 4 shows the mode of application.

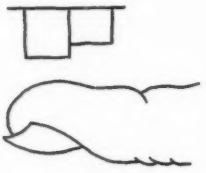


FIG. 3.

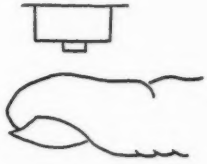
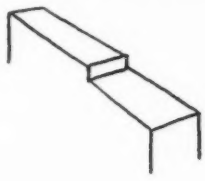
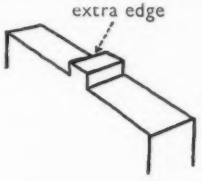


FIG. 4.

Blade-step objects (L).—These are squares of acrylic 0·32 cm. thick and of side 2 cm. The sides are milled to leave steps of measured depth as fig. 5 shows. The control-object is a flat blade. This test, confined to





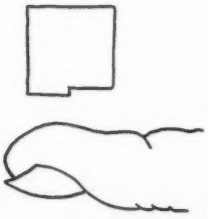


FIG. 5.

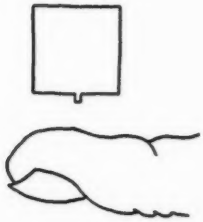


FIG. 6.

the finger-tip, was begun with a step of 0·5 mm., and decrements of 0·03 mm. were made until the threshold was determined.

Blade-peg objects (M).—These consist of acrylic squares 0·32 cm. thick and side 2 cm., which are milled to leave small pegs protruding as fig. 6 shows. The pegs are 1 mm. long and of various depths. The control-object is a flat blade. This test, also confined to the finger-tip, was begun with a peg of depth 0·38 mm. and decrements of 0·03 mm. were made.

Concave-blade object.—This is cut from paste-board to fit the silhouette of the subject's finger-tip and was applied as fig. 7 shows. It was used in a few subjects to demonstrate that the curvature of the object is easily felt when it is placed perpendicular to the finger-tip.

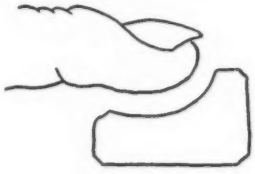


FIG. 7.

Test-objects and Procedure for Sharp-Blunt Discrimination (O)

The test-objects are strips of acrylic 1 cm. long and of various thicknesses. These were used on the dorsum of the hand. The control-object is a steel blade 0·05 mm. thick. The other test-object is a hatpin with a rounded head of 4 mm. diameter, and this was used on the palm.

Test-object for Touch

The Æsthesiometer described by Renfrew (1960) was used in tests on finger-tip, first phalanx and palm.

Test-objects for Muscle-joint Sense

The micrometer-peg objects (G) were adapted for use in this test by fitting them with flat-ended brass pegs of 4 mm. diameter, and they were used in conjunction with the frame (P). The subject placed the tips of his index, middle and ring finger on three small holes on the platform of the frame. The holes are in a straight line at intervals of 2·54 cm.

The objects were pushed quickly up into contact with the three fingers lifting them off the frame a little. The initial protrusion of the middle peg was 4 mm. and decrements of 0·5 mm. were made in the course of the test.

RESULTS

(1) Below threshold levels incorrect identification of control-objects was as frequent as incorrect identification of test-objects. Thus, for

example, one point was identified as two-points as frequently as two-points were identified as one point.

(2) The thresholds for surface space in terms of two-point, shape, direction and size discrimination are given in Table I, and for each site there is a close similarity between the thresholds. The thresholds rise progressively between the finger-tip and the dorsum of the hand. The ratio of average thresholds for finger-tip, first phalanx and palm is 1·0 : 2·3 : 3·9.

TABLE I.—EXPERIMENTS INTO SURFACE SPACE

Thresholds in mm.

		*Subjects**										
Site	*Test*	1	2	3	4	5	6	7	8	9	10	*Average*
Finger-tip	two-point	2	2	2	3	1	2	1	2	2	2	1·9
	direction	2	2	3	2	2	3	2	2	2	2	2·2
	size	2	2	2	2	2	2	2	2	2	2	2·0
	shape	2	2	1	1	1	3	2	2	1	2	1·7
First phalanx	two-point	4	4	5	5	5	6	4	4	3	4	4·4
	direction	5	5	6	5	4	7	3	6	3	3	4·7
	size	3	4	3	5	5	5	4	6	3	6	4·4
	shape	3	4	5	4	4	5	5	5	4	5	4·4
Palm	two-point	5	8	8	8	6	7	6	7	6	6	6·7
	direction	6	10	9	11	6	10	3	7	8	6	7·6
	size	6	7	8	7	7	9	6	10	5	11	7·6
	shape	8	6	7	10	8	12	8	8	9	7	8·3
Dorsum	two-point	13	10	14	15	17	18	17	11	10	10	13·5
	shape	13	12	12	15	21	20	20	7	11	11	14·2

*The figures in each column apply to one subject.

TABLE II.—EXPERIMENTS INTO SURFACE SPACE

The shape test with variations in the length of the base of the triangle; thresholds in mm.

Subject	*Site*	*Base cm.*	*Threshold mm.*
1	1st phalanx	2	3
		4	2
2	1st phalanx	2	3
		6	3
3	palm	2	9
		4	9
4	palm	2	7
		4	7
5	palm	4	7
		6	7
		12	7

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(3) In Table II it is shown that the shape discrimination threshold is given by the amplitude or height of the triangle formed by the three points of the test-object, and is not related to the length of its base or the size of its angles.

(4) Only one subject was tested with the hinge object (E) on the palm. His threshold was 5 mm. while his two-point threshold was also 5 mm. (subject 1 in Table I). Two subjects were tested on the palm with the curved object (F) and their thresholds were 6 mm. and 8 mm., while their two-point thresholds were both 8 mm.

(5) When the micrometer-blade object (J) was set at 0·75 mm. the subjects said that their first feeling was a difference of the levels of the blades. Lower than 0·5 mm. this feeling was lost and the subjects discriminated the test-object from its control by the feelings of pressure of the two blades or by the feeling of a corner or line between the two blades. This discrimination was, to the subjects, distinct from the feeling of levels and will henceforth be referred to as Touch Feeling Discrimination.

(6) When the blades of the object, which is the control of the micrometer-blade object, were separated by 0·5 cm. and pressed on the finger-tip some subjects had an illusion that the proximal blade was at a higher level than the distal blade.

Table III shows the thresholds obtained with the micrometer-blade object, the blades being separated by 0·5 cm. Blades of 0·08 cm. and 1·27 cm. thickness were used. There is a considerable range of thresholds. On questioning the subjects after the tests, it appeared that some gave their attention to the feeling of levels and were misled by the tactile illusion described above. Some subjects concentrated on the Touch Feeling Discrimination and were thus able to achieve better results. The scatter of results is probably to be explained in this way.

(7) With the micrometer-peg object (G) on the finger-tip there was a narrow range of thresholds as shown in Table III. With the control object the middle peg was felt, by some subjects, to be at a higher level than the other two, but this illusion did not make the discrimination more difficult. In this test the threshold is given by the amplitude or height of the triangle, the base of which is formed by the line joining the two outside pegs, and the apex by the middle peg. The test is thus analogous to that of shape discrimination in surface space.

(8) With the curved blades (H) there was a narrow range of thresholds as shown in Table III. The range is similar to that obtained with the micrometer-peg object. Some subjects had the illusion that the control-object was concave, but this did not make the discrimination more difficult.

TABLE III.—EXPERIMENTS INTO DEPTH SPACE

Tests on the finger-tip; thresholds in hundredths of mm.

Method	*Thresholds in ten tests**											
	1	2	3	4	5	6	7	8	9	10	*Range*	*Average*
Micrometer-pegs	100	75	100	75	100	75	50	75	50	75	50–100	78
Micrometer-blades, separated, 0·5 cm. thick												
0·08 cm. thick	100	75	63	25	63	50	125	25	50	125	25–125	70
„ „ „ 1·27 cm. thick	13	50	13	38	38	50	50	100	63	38	13–100	45
Curved blades	50	75	75	63	75	75	75	63	75	100	50–100	73
Micrometer-blades, together, 0·08 cm. thick	38	50	38	38	50	50	38	50	25	50	25–50	43
„ „ „ 0·16 cm. thick	38	38	50	50	25	38	50	50	63	63	25–63	47
„ „ „ 0·64 cm. thick	38	25	25	25	25	25	38	25	25	38	25–38	29
„ „ „ 1·27 cm. thick	13	13	25	13	13	13	13	13	13	38	13–38	17
Cylinder-peg, 2·54 cm. circumference ..	13	13	7·5	7·5	7·5	7·5	7·5	7·5	7·5	7·5	7·5–13	8·6
Blade-steps, 0·32 cm. thick	48	35	45	30	38	28	30	30	35	48	28–48	37
Blade-pegs, 0·32 cm. thick	20	20	28	15	20	15	20	20	15	23	15–18	20

*The figures in each column do not necessarily apply to one subject.

(9) When the blades of the micrometer-blade object (J) were together the range of thresholds was small. It is evident in Table III that the thresholds, which are those for Touch Feeling Discrimination, are related to the thickness of the blades. With blades thicker than 0·32 cm., that is, greater than the surface space threshold, there is a steady drop in the threshold, that is, the relation is between Surface Space *Feeling* and Touch Feeling Discrimination. The cylinder-peg object gave the lowest thresholds.

(10) The ratio of the threshold found with the blade-peg objects to the threshold found with the blade-step objects is 1 : 1·8. The pegs have an extra edge which comes into contact with the skin (*see* fig. 6). The ratio between the total length of the edges of the peg, and the length of the edges of the step is 1 : 1·6. The thresholds from these tests which are tests of Touch Feeling Discrimination appear to be related to the length of the edge in contact with the skin.

(11) The micrometer-blade object (J) could not be used proximal to the finger-tip for the inelasticity of the skin prevented the blades being brought into contact with the skin along their entire lengths. However, thresholds for the micrometer-peg object (G) were found in first phalanx and palm and are given in Table IV. The ratio of average thresholds for finger-tip, first phalanx and palm is 1 : 2 : 3·1.

TABLE IV.—EXPERIMENTS INTO DEPTH SPACE

The micrometer-peg test on first phalanx and palm
Thresholds in hundredths of mm.

	Subjects										
Site	1	2	3	4	5	6	7	8	9	10	*Average*
First phalanx	100	150	250	150	150	150	150	150	150	150	155
Palm	189	250	250	250	189	250	250	325	189	250	239

(12) The concave blade (fig. 7) was used in only a few subjects since the results are obvious. The feeling of the concave curve is pronounced although there are no variations of touch feeling along its entire length.

(13) In the tests of sharp-blunt discrimination ten subjects could distinguish the two ends of the pin on their palm. With the acrylic blades on the dorsum of the hand, ten subjects gave thresholds between 0·5 mm. and 1 mm.

(14) The thresholds for joint sense in five subjects were: 2 mm., 3 mm., 3 mm., 3·5 mm., and 3·5 mm.

(15) The thresholds for touch feeling in ten subjects were either similar in the finger-tip and palm or were lower in the latter.

GENERALIZATIONS FROM RESULTS

(1) In surface space there is one threshold, at any one site, which is common for two-point, shape, direction and size discrimination.

(2) In depth space a clear line cannot be drawn between Touch Feeling Discrimination and space feeling. On the basis of introspection of the subjects it is probable that the thresholds given by the micrometer-peg object (G) and the curved blades (H) are those of space feeling. The ratio of thresholds between finger-tip, first phalanx and palm is roughly the same for surface and depth space. The ratio of surface space threshold to depth space threshold is almost 3 : 1.

The threshold of both surface and depth space sense is to be measured, not in terms of areas or angles, but in terms of the length of a line or rather the distance between two points. One point is the site of a touch feeling but the other one may be a geometrical point which is not the site of a touch feeling. In other words, the threshold of space is not necessarily the distance between two points of touch feeling.

(3) There is no correlation between depth space threshold and touch feeling threshold. Neither is there a correlation between surface space threshold and sharp-blunt discrimination.

(4) Joint sense threshold is considerably greater than dermal space sense threshold in the finger-tip.

(5) Within the limit of size of our test-objects, the threshold for Touch Feeling Discrimination varies inversely with the breadth of the test-object, provided this is greater than the surface space threshold.

(6) The spatial aspects of objects can be felt in the absence of variations of touch intensity (Touch Feeling Discrimination) as was shown by the concave cardboard object. This suggests that there is an image of space. This image probably introduces tactile illusions into depth tests.

Discussion

For the purpose of our experiment we divided space into two planes. It now remains for us to synthesize these planes in such a way that our particulate results and observations will be given some cohesion. This we hope will confer on space an individuality, so to speak, distinct from touch. The evidence will be discussed in terms of three methods of investigation namely, introspection, experiments on normal subjects, and clinical study.

Introspection.—If the blunt point of a pencil is pressed on the palm and the feeling analysed it is discovered that two statements can be made by the subject. First, "I am being touched," and second, "something is touching me." These statements, in terms of the passive and active forms of the verb *to touch*, reflect the subjective and objective aspects of sensation. Although the feeling of being touched is unequivocal, the awareness of something touching is not so certain and it is impossible to be sure that the awareness of the object is anything more than an inference. Nevertheless continued introspection reveals that the attention cannot be

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given simultaneously to the touch feeling and the object although the subject can apparently deflect his attention from one to the other. We admit, however, that the subject's ability in this respect may depend on his skill and training in introspection.

Should the object exceed in size the surface space threshold, the attention of the subject is spontaneously directed to the object. This can be experienced fairly convincingly by setting the points of a compass to six or seven millimetres and running the points down the palm and index-finger to the finger-tip. If the subject allows his attention to float, it passes at the base of the finger from the skin to the exterior as soon as the feeling of one point gives way to a feeling of two points. This at first sight would seem to indicate that space feeling extinguishes touch feeling but of course this is not the case. When a coin is held between the fingers the subject is aware of its hardness and a moment's reflection shows that this hard or resistant feeling is a touch feeling displaced from the skin into the object. Indeed, it requires an effort of introspection to ignore the space of the object and return the touch feeling to the skin. Clearly space feeling displaces touch feeling outwards causing it to be interpreted as resistance and, although both cannot be attended to simultaneously, the mixture of the two feelings which ensues has, we believe, induced people who study sensation to conclude that the feelings evoked by the contact of an object are homogeneous. To suppose, however, that because two feelings are always associated they are the same feeling is an example of the Reductive Fallacy, a fallacy which has trapped only physiologists for people in general can, and in fact they are obliged to, separate the two feelings as is evident when they say that objects feel square or round, and that they feel hard or soft.

A peculiar feature of dermal sense is the readiness with which space is inferred from touch feeling. For instance, it is commonly supposed that movements of the skin can be felt but evidence to the contrary is presented when someone (a subject cannot test himself) slowly presses the point of a pencil on the pulp of the subject's finger-tip. The increasing intensity of the touch feeling leads to the inference that the skin is moving for the skin is often seen to be moving in similar circumstances. Introspection fails completely to persuade the subject that there is a feeling of skin movement or, for that matter, that there is a feeling of the pencil moving. When the object exceeds in size the surface space threshold there is still no feeling of skin movement but in this case the object is felt to move. In short the only movement in depth, and also on the surface, experienced in dermal sense is attributed to the object.

This inability to feel skin movement calls for a review of the test of Pinch-Press Discrimination (Renfrew and Cavanagh, 1954). It was originally thought that the subject felt the skin moving or felt the fold of skin held between the examiner's fingers, a sort of skin postural sense.

Neither is true. When the subject's skin is pinched he feels the pressure of the examiner's fingers and on either side of this a tight, stretched feeling in the skin. This tight feeling we suppose is a touch feeling which is diffuse and rather faint. It is absent when the examiner only presses the skin. Whether a loss of pinch-press discrimination is to be attributed to a loss of this touch feeling or to a raising of the surface space threshold rendering the subject unable to discriminate the pressure of the examiner's finger from the tight skin feeling, we do not know. The former may be true since there is no marked regional variation in this type of discrimination; but the latter explanation appeals more since pinch-press discrimination correlates well with two-point discrimination. The latter explanation makes it apparent, too, why this test, which seems so crude, is in fact very sensitive. Apart from this, however, is the point that, when a subject says his skin is being pinched, he is making an inference on the basis of visual experience or on the basis of pinching himself.

Experiments on normal subjects.—The ready inference of space from touch feelings presented a constant problem in our experiments. That there is a feeling of space is certain but where an inference of space ends and a feeling of space begins cannot be decided with any degree of precision. For instance, in the discrimination of sharpness from bluntness the subject will confidently infer, on the basis of visual experience, that the object which evokes a blunt feeling is thick and the object which evokes a sharp feeling is thin. To the examiner it may seem that the subject is having spatial feelings and indeed Head supposed that in discriminating the sharp and blunt ends of a pin his subjects were feeling size. Introspection by the subjects reveals the error in this supposition and there is also the objective evidence that the threshold for sharp-blunt discrimination is very different from surface space thresholds measured by other techniques. Our conclusion is that the discrimination of sharpness from bluntness is based on the quality or intensity of touch feeling and not on space.

A similar state of affairs obtains in depth space. When the micrometer-blade object is brought into contact with the skin the projecting corner of the step produces a touch feeling which allows the inference of the step. Should the step exceed the depth threshold the subject is immediately aware of the two levels of the test object and no inference is involved. However the dividing line between inference and feeling cannot be accurately determined and it is necessary to rely on the introspection of the subjects. Unlike surface space there is, unfortunately, no objective evidence which will bring out the distinction between feeling and inference.

We have shown that the threshold for two-point discrimination is similar to the threshold for size discrimination. It follows that when the surface space threshold is reached the subject becomes aware of two opposite surfaces of the test object irrespective of whether the object is

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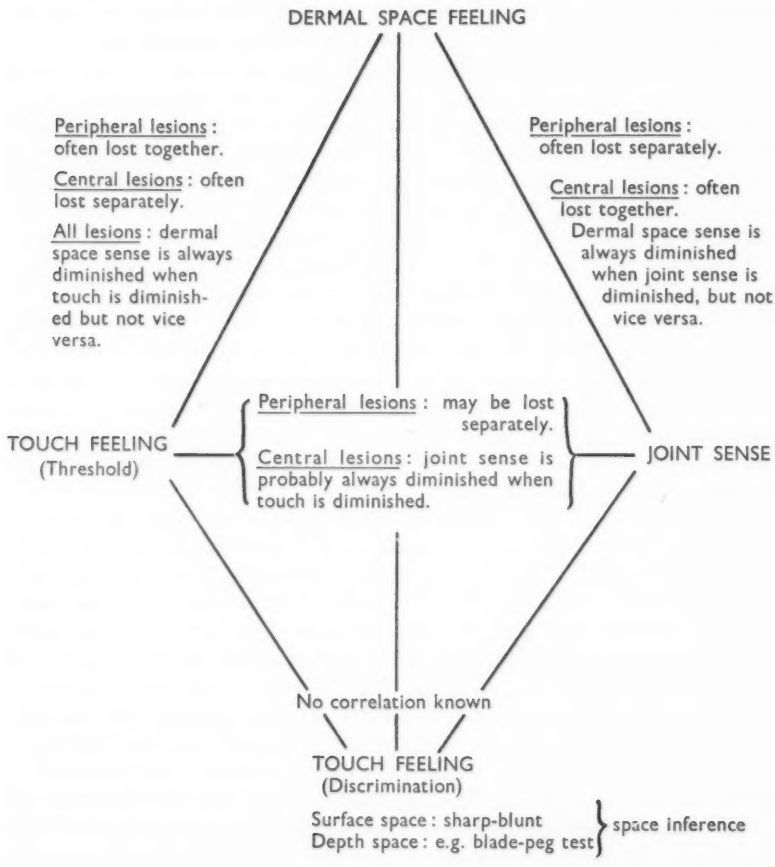
solid or whether there is a space between these two surfaces. Tests of surface space threshold can thus be reduced to tests of the threshold of two-plane discrimination, the planes being perpendicular to the skin. This brings out the essential similarity between surface and depth space for in testing depth space the subject is asked to discriminate two planes, these planes being parallel to the skin surface. All spatial tests can therefore be referred to as tests of two-plane discrimination.

The identity of space sense as distinct from touch sense is established, we think, by the following points. The surface space threshold is a constant, independent of the method of testing although related to the

CORRELATION OF TOUCH FEELING AND SOMATIC SENSE OF SPACE


DERMAL SPACE FEELING
Peripheral lesions: often lost together.
Central lesions: often lost separately.
All lesions: dermal space sense is always diminished when touch is diminished but not vice versa.
Peripheral lesions: often lost separately.
Central lesions: often lost together.
Dermal space sense is always diminished when joint sense is diminished, but not vice versa.
TOUCH FEELING (Threshold)
Peripheral lesions: may be lost separately.
Central lesions: joint sense is probably always diminished when touch is diminished.
JOINT SENSE
No correlation known
TOUCH FEELING (Discrimination)
Surface space: sharp-blunt
Depth space: e.g. blade-peg test
space inference

region of skin tested. Similarly the depth space threshold is also a constant although Touch Feeling Discrimination tends to confuse this. Surface and depth space thresholds bear a relationship to each other, the latter being roughly a third of the former. Lastly, and most important, the gradient of space threshold between the finger-tip and palm is not paralleled by the touch feeling threshold which is similar in the finger-tip and palm.

It is worth noting that, when the size of an object is less than the surface space threshold, the subject is unable to feel the relative depth levels of its parts. This is a necessary truth for it is clear that an object which is felt as point cannot be felt to have variations in depth. Thus the surface space threshold determines whether or not the subject will have a depth appreciation with respect to a particular object brought into contact with his skin. Consequently a rise of surface space threshold from the normal two millimetres to ten millimetres will render the finger-tip almost useless with regard to depth awareness. The importance of depth sense can only be guessed. This highly developed sense, more highly developed than joint sense, cannot be without purpose and its loss can hardly leave the efficiency of the fingers unimpaired. For instance, clumsiness with pencil, coins or buttons may be partly explained by a loss of this sense.

Clinical study.—Head and Thompson (1920*b*) drew attention to various correlations between touch, two-point discrimination and joint sense. We have shown these in diagrammatic form, substituting dermal space sense for two-point discrimination for we have found that a rise of space threshold is common to all forms of testing. Most of the correlations are amply confirmed by everyday experience in neurology.

The division of peripheral nerves to give separate branches to skin and joints, and the coarseness of tests of joint sense, probably explain a good many of the correlations. However, it is to the relation between touch feeling and space feeling that we wish to draw particular attention. The puzzling feature of this relation is that, as far as we know, space feeling may be reduced while touch feeling is undisturbed, although space feeling is always reduced when touch feeling is reduced. The latter part of this statement Head explained away by saying, "It is obvious that a diminution of tactile sensibility will diminish the ease with which two points are discriminated." But this is not obvious. Moreover the statement that it is obvious will not function as an explanation.

This curious correlation between space and touch feelings raises the problem of the anatomical and physiological basis of space feeling. It is probably true that a spatial pattern of stimulation in skin and retina is maintained in the spatial arrangement of neurones in the peripheral and the optic nerves. It is, however, straining credulity too far to suppose that a circle of light falling on the retina leads to the activation of a circle

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of neurones in the cerebrum. If a spatial feeling is therefore not a reflection of a spatial arrangement of neurones it follows that it is causally related to the activation of specialized neurones, a view which, on the assumption that space feeling is sensational, is in accordance with Müller's doctrine of Specific Nerve Energies.

Having postulated that special neurones subserve space feeling it seems natural to suppose that there may be special space receptors in the skin. The functions of many of the sensory "end-organs" of the skin remain obscure, but, since the existence of joint receptors which give rise to feelings of posture and movement is now accepted, some of the skin receptors could well give comparable spatial information. On the other hand, it may not be necessary to postulate separate receptors for space feeling and touch feeling, for there is no reason to suppose that one receptor does not innervate two neurones. In this connexion it is interesting to speculate on the innervation of Meissner's corpuscles, which are known to have one or more myelinated fibres, and also one or more unmyelinated fibres connected to them.

It is commonly supposed that one system of receptors and pathways can do duty for both touch and space feeling, but it is evident that one system allows no explanation of the strange differential loss of these feelings which occurs in disease. It is true that two systems of receptors and pathways do not at the moment allow an explanation in physiological terms, but two pathways, with a single or double system of skin receptors, can be regarded as a minimum requirement. Possibly some special connexion between the touch feeling pathway and the space pathway is required, either in the dermal plexus, or by intercalated neurones in the cord.

It may, of course, be asked at this point, "What is the nature of the stimulus which activates space receptors?" To say that space *per se* can cause a receptor to discharge does not seem convincing. But questions such as this pose two separate questions, one in the realm of philosophy or logic, and the other in the realm of psycho-physiology. Both must be answered separately. To the first it may be answered that, adopting the philosophy of Idealism, the cause of any mental experience will remain for ever unknown, and that space feeling presents no greater mystery than light and touch feelings. To the second it may be answered that any object of sufficient size pressed on the skin constitutes an adequate stimulus of space receptors. The original question, therefore, is not so devastating as it first appears.

Whatever effects our speculations on the structures underlying space feeling have on physiologists, it seems to us that the theory of two pathways, one for space feeling and the other for touch feeling, has something to recommend it to clinicians. There is considerable evidence

that lesions of the posterior columns and of the parietal lobes result in a diminution of dermal space and joint senses. It is not inaccurate, therefore, to say that the posterior columns and the parietal lobes subserve somatic space sense, whatever other functions they have. This leads to the theory, which is attractive if only for its simplicity, that the posterior columns and the pyramidal tracts, which run parallel courses and have their end stations adjacent in the cerebrum, are the afferent and efferent sides of one system. In this system, the posterior columns carry the function of space feeling and the pyramidal tracts the function of space acting. The somatic sense of space we have termed *chorœsthesia* and this allows the terms dyschorœsthesia and achorognosia, the former being the sensory counterpart of paresis and the latter the sensory counterpart of apraxia.

The term dyschorœsthesia can be applied no matter what spatial tests have been used since, as we have shown, all the tests can be regarded as tests of two plane discrimination. Nothing is gained by the multiplication of spatial tests or by the multiplication of the names of senses examined by such tests. Moreover the inference of the site of the lesion responsible for raising the threshold of any of the tests is the same. The essential problem is to discover the best test for clinical use, weighing sensitivity against suitability for routine practice.

SUMMARY

(1) A distinction is drawn between dermal space feeling and touch feeling on the basis of introspection.

(2) Space is divided into a plane parallel to the skin surface and one perpendicular to it. Several methods of measuring thresholds of space feeling are described.

(3) The results reveal that there is a constant threshold for each plane depending on the region tested and that the depth threshold is roughly a third of the surface threshold.

(4) A distinction is drawn, on the basis of the results, between Space Feeling and Touch Feeling Discrimination. There is no correlation between them except that surface space feelings determine the threshold for Touch Feeling Discrimination.

(5) Differences between dermal space feeling and touch feeling are discussed on the basis of introspection, experiments on normal people and clinical study.

(6) The problem of the anatomical and physiological basis of space feeling is discussed.

(7) Dermal space sense and joint sense are combined to form the Somatic Sense of Space. This is called chorœsthesia. It is suggested that dyschorœsthesia is the sensory counterpart of paresis.

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ACKNOWLEDGMENT

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HEREDOFAMILIAL MONONEURITIS MULTIPLEX WITH BRACHIAL PREDILECTION

BY

RICHARD A. TAYLOR[1]

INTRODUCTION

THE purpose of this paper is to report, in detail, an unusual family covering five generations. Afflicted members develop one or more attacks of acute brachial neuritis or mononeuritis multiplex characterized by excruciating pain, severe weakness, atrophy, and sensory loss. They typically recover completely or regain useful function. Both males and females are affected, but attacks associated with pregnancy are characteristic. There is no known incidence of consanguinity.

Further, an hypothesis is advanced that through this family may run a genetically determined substrate or diathesis which manifests itself as hyperergic reactions to manifold stress. This family may serve to link a wide spectrum of tissue responses which have a similar genetically determined basis.

REVIEW OF LITERATURE

Genetically determined polyneuropathy which may have recurrent manifestations, although rare, is well known. The two most commonly cited types are interstitial hypertrophic polyneuritis of Dejerine and Sottas, and heredopathia atactia polyneuritiformis (Refsum's syndrome). These conditions are typically manifested by a gradually progressive polyneuropathy beginning early in life, but recurrent relapsing attacks have been reported by Harris and Newcomb (1929); Nattrass (1921); and André-van Leeuwen (1943). It is apparent, however, that the family reported here does not fulfil the diagnostic criteria for either of these syndromes as outlined by Olesen (1957) and Fleming (1957).

Recently Austin (1958) reviewed a type of recurrent polyneuropathy affecting young adults which was symmetrical in distribution, most pronounced distally, and chiefly motor. Cranial nerves three, six, seven, and nine were often affected. Pain was not a prominent feature and there was no genetic determination. Because of these features,

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Austin's cases are not similar to those in this report. Furthermore, he excludes Ungley's 3 cases (1933), who are identical to the females reported here, because they are atypical of the syndrome he describes.

Exclusive of instances of sciatic or cranial nerve implication, the neural involvement in this family closely resembles, or is at times identical with, acute brachial neuritis. Reported cases of acute brachial neuritis were unusual before 1942. Between 1942 and 1950, 200 cases were reported in the Anglo-American literature. Olle Höök (1950) added 8 cases, characterized by sudden excruciating pain in the shoulder, radiating down the arm, followed by weakness and atrophy. He mentions the close resemblance of his patients to those with serum neuritis or with periarteritis nodosa. None, however, was familial.

To my knowledge, only three reports comparable to the present communication exist. Dreschfeld (1886), in discussing some rarer forms of muscular atrophies, reported a 43-year-old female who suddenly experienced pain in her right wrist and hand, especially the little and ring fingers, followed by a wrist-drop and paralysis of her arm. The shoulder became more affected than the elbow and the whole arm was very painful. Fourteen days later the left arm became affected. She eventually recovered. She had two recurrent attacks, ushered in by pain, which were less severe. The patient's sister had seven similar attacks.

Davies (1954), in reporting a family with recurrent peripheral nerve palsies, mentions a family described by Ross and Bury (1893). One sister, at the age of 25, noticed weakness of her hand associated with severe pain between her shoulders. She recovered in three weeks. During the next nine years she had several similar attacks. Her last attack involved the anterior leg muscles and intrinsic muscles of her foot with sensory loss over her foot and lateral aspect of her leg.

Her sister, at the age of 43, developed pain in her right hand followed by weakness of the right upper extremity. Two weeks later the opposite limb became affected. There was severe pain across the shoulders and paræsthesiæ of her hands. She eventually recovered.

Davies' family, covering five generations, differs from the family of Ross and Bury and the one constituting this report in that pain was never a feature, the weakness was of relatively short duration, and sensory findings were minimal. His family appears similar to one reported recently by Wahle and Tönnis (1958) in which there is an apparent familial sensitivity to peripheral nerve damage due to pressure.

Ungley (1933) reported a mother and her two daughters who had a syndrome clinically identical to female members of the family forming the basis of this report. They suffered attacks of lower motor neuron paralysis of irregular distribution, preceded and accompanied by sensory disturbances and pain, which showed a pronounced tendency to appear

or recui after childbirth. The mother developed unilateral wrist-drop at the age of 39, a few days after the termination of her fifth pregnancy, having suffered from severe pains in the affected arm for three months beforehand. Similar pains had occurred at the age of 26, but without loss of power. Twenty-one years later there was some residual paralysis of the extensors of the wrist and fingers.

The younger daughter, at the age of 23, suffered from similar pains in one shoulder and arm during the latter months of her first pregnancy, with rapid involvement of the other limb after parturition. Subsequently the upper limbs showed asymmetrical wasting of peculiar distribution, with localized areas of anæsthesia. Gradual but almost complete recovery followed.

The other daughter, at the age of 29, developed severe pains in the right shoulder and arm, followed, soon afterwards, by wrist-drop and paralysis of the small muscles of the hand on the affected side. Pains and localized anæsthesia occurred in the opposite arm. She recovered, but two weeks after the birth of her child, pains recommenced in both shoulders with paresis of both deltoid muscles. Wrist-drop again developed, this time on the left side, and was followed by extensive but asymmetrical wasting of both shoulder girdles and of other muscles of the upper extremity. The subsequent recovery was almost complete.

Sensory loss, as in the cases reported herein, was not of the glove and stocking type, but was confined to small areas of unusual distribution which tended to remain after recovery from the paralysis.

X-rays of the spine and laboratory studies of the cerebrospinal fluid, gastric contents, blood and urine were normal. Hæmatoporphyrinuria[1] was not a feature.

The Propositus

A 16-year-old white male was admitted to the University Hospital on September 8, 1958, because of pain and weakness of the right upper extremity. During the summer he had worked at baling hay, but denied knowledge of trauma to his neck or arm. His illness began approximately seven weeks prior to admission when he became hoarse. Three weeks following the hoarseness he noticed a dull ache in the region of his right deltoid which, in a few days, progressed to involve the arm to the elbow. Three days after the onset of pain he was unable to elevate his right upper extremity above his head. The pain was a constant, severe, sharp ache which soon affected the forearm and hand. Superimposed upon the constant ache were sharp stabbing pains which radiated down the forearm into the first three digits, always sparing the fourth and fifth. Soon the entire arm became weak. Three weeks before admission he experienced a ten-day period of urinary dribbling after voiding, but stated that sensation in his bladder was preserved and that he had a feeling of complete emptying after voiding.

At the age of 6 years he had rheumatic fever. He was out of school for eight weeks. He remembers having pain in his arms and a fever. He was treated with

[1]This is the term used in the original article.

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daily injections of penicillin and bed rest. He reported at least two spontaneous episodes of nose bleed every year since the age of 6 or 7.

On September 5, 1958, he had been hospitalized elsewhere. The cerebrospinal fluid (C.S.F.) contained a total protein of 75·9 mg. per cent, a sugar of 62 mg. per cent, and a chloride of 131 mEq./litre. The erythrocyte sedimentation rate (ESR) was 7 mm. and 2 mm. per hour on two occasions. Serum electrolytes, urinalysis, fasting blood sugar and B.U.N. were normal. The hæmoglobin was 13·2 grammes, the W.B.C. 9,050 with 1 basophil, 1 band, 60 adult polys., 35 lymphocytes and 3 monocytes. X-rays of the skull, chest, and cervical spine were negative.

Physical examination on September 8 showed him to be well developed and well nourished, but in obvious pain. His voice was hoarse. He held his right upper extremity splinted against his body. The temperature was 98·6° F. and the blood pressure 130/70. Blood pressures taken four times a day for a period of twenty-six days ranged between 140 systolic and 70 diastolic. He had generalized lymphadenopathy. The heart and lungs were normal. The cardiac consultant found no valvular disease. Indirect laryngoscopy showed paralysis of the right vocal cord.

Neurologically the patient had a complete Horner's syndrome on the right. The left upper extremity and both lower extremities had good strength, tone, and function without sensory deficits. In the right upper extremity were atrophy and severe weakness of the deltoid, supra and infraspinati, and latissimus dorsi; moderate atrophy and weakness of the biceps, triceps, brachioradialis, supinator of the forearm, extensors of the wrist and thumb, and the flexor carpi ulnaris; slight weakness of the finger flexors, lumbricales, and interossei. The right supra- and intrascapular region, a strip down the back of the arm for about 8 in., and the first dorsal interosseus space were hypæsthetic and hypalgesic. Position and vibration sensibilities, and two point discrimination were intact. Sweating was lost over the right first dorsal interosseus space. Sweating was normal and equal otherwise on both sides of the body except for the anhidrosis of the right side of the face. The muscle stretch reflexes were absent in the right upper extremity, but present and physiological elsewhere. The abdominal, corneal, gag, and plantar reflexes were normal. Adson's manœuvre caused no obliteration of the radial pulses. The nerves were not enlarged. The right median nerve was tender to compression at the elbow, and on percussion pain radiated into the forearm and hand.

For three days after September 11 he had pain in the medial aspect of his right thigh near the knee. Two days later he noticed a constant ache in the region of the left deltoid which, by September 16, was severe and persistent. The left median nerve was tender to palpation at the elbow. This left sided pain subsided gradually three weeks after its onset. He required 75 mg. of Demerol every three or four hours for relief of pain.

On September 10 a left inguinal node was biopsied. Cultures of the specimen for tubercle bacilli and fungi were negative. The specimen showed hyperplasia of the reticulo-endothelial cells and supported a diagnosis of chronic lymphadenitis. Because of the possibility of a lymphomatous invasion of the brachial plexus, a bone-marrow biopsy was undertaken. Throughout the marrow were numerous lymphoblasts. They had a normal chromatin pattern and were not of leukæmic type. No lupus erythematosis cells were seen and no neoplastic alterations were observed. The hæmatologist's impression was lymphoblastic reaction, cause undetermined. These results were highly suggestive of infectious mononucleosis. Subsequent heterophile agglutinations (1 : 224) were compatible with this diagnosis.

Audiometry showed no significant organic hearing loss in either ear. On ophthalmologic examination the discs and fundi were normal.

During hospitalization the patient gradually improved. On October 27 he had little or no pain and was not requiring analgesics. He had fair strength in dorsiflexion

of his wrist. The Horner's syndrome was improving and his voice less hoarse. He still complained of numbness over the right first dorsal interosseus space and the posterolateral aspect of his arm to the elbow. He was discharged October 27, 1958, with instruction to return to the out-patient clinic.

X-rays: P.A. of the chest, A.P., lateral and oblique views of the cervical spine were normal. A.P. views of the forearms, wrists, knees, ankles, and shoulders failed to demonstrate evidence of epiphyseal dysplasia. Myelography, including the cervical region, was normal.

EKG and EEG: Normal.

EMG (Philip T. White, M.D.):

"Coaxial needle explorations were undertaken in both upper extremities. In the right deltoid numerous fibrillations ranging anywhere from 10 to more than 100 microvolts were seen. Spontaneous fasciculations were noted throughout the muscle. There was abnormal irritability of the musculature with repetitive rhythmic motor units being set off by movement of the needle and persisting an abnormally long time. On voluntary effort, there was a marked decrease in both the amplitude and number of motor units. A similar response was noted in the right biceps brachii, brachioradialis and first dorsal interosseus. The abnormal findings were more pronounced in the proximal musculature with fewer fasciculations and fewer fibrillations being noted in the hand muscles. The muscles of the left upper extremity did not reveal any spontaneous abnormalities, and the pattern on voluntary effort was normal. In the lower extremities some questionable fibrillations were noted in the right anterior tibial muscle but no fasciculations were seen, and on voluntary effort, the pattern was normal. No abnormal wave forms were found in the gastrocnemius muscles or the left anterior tibial muscle.

Conclusions.—The changes seen suggest a neurogenic lesion in the right upper extremity, most pronounced in the proximal musculature. Some myogenic abnormalities may be present, but, in general, the picture is that of a neurogenic disturbance. There are no changes suggesting a myopathy."

Deltoid muscle biopsy (W. Musser, M.D.):

"The specimen is received in formalin and consists of two small specimens of muscle and attached skin. Microscopically, one is struck with the basophilia of many of the muscle fibres. The sarcolemmal cells with prominent nucleoli are quite distinct, apparently due, in part, to shrinkage of cells. The degenerated muscle fibres are separated by a small quantity of loose connective tissue that has been sparsely infiltrated by lymphocytes and plasma cells. The vascular spaces noted in the connective tissue stroma are unremarkable. Vacuoles are noted in many muscle cells. The overlying skin included with the specimen is unremarkable."

Laboratory data.—Kolmer and Kahn negative. Hæmoglobin 15·3 grammes. White blood count 11,950. Differential: 11 stabs, 50 adult polys., 33 lymphocytes, 5 large monocytes. Erythrocyte sedimentation rate 15 mm. per hour (corrected); subsequent determinations normal. Heterophile titre: positive through 1 : 224 (normal below 1 : 56). (Guinea-pig absorbed, positive 1 : 112; red cell absorbed 0.) September 29 positive through 1 : 224 and October 8 positive through 1 : 112.

Serum bilirubin 0·4 mg. Cephalin flocculation negative. Alkaline phosphatase 8·6 K and A units. Total serum protein 7·8 grammes; albumin 4·99 grammes; globulin 2·81 grammes. Thymol turbidity 5·5 and 2·5. Serum calcium 9·9 mg. per cent. Potassium 5·0 mg. per cent. Sodium 138 mEq./litre. B.U.N. 7 mg. Total cholesterol 144 mg. per cent. Blood creatine: 2·44 and 2·9 mg. (normal 6 mg.). Urine creatine: 78·9 mg. per twenty-four hours (normal 200 mg. per twenty-four hours). Total volume 2,630 c.c. Creatinine: 0·7 mg. (normal 1–2 mg.). Urinary creatinine 620 mg. per twenty-four hours (normal 1–1·8 grammes per twenty-four

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hours). Fasting blood sugars 71 and 79 mg. per cent. Two-hour post-prandial blood sugar 73 mg. per cent.

Cerebral spinal fluid (C.S.F.) September 9: 1 W.B.C., 397 R.B.C., globulin (Pandy) very faint trace. Sugar 74 mg. per cent. Total protein 83 mg. per cent. C.S.F. October 3: Total protein 50·5 mg. per cent. A control at another laboratory revealed a total protein of 34 mg. per cent. Colloidal gold curve 4332210000. Kolmer: non-reactive.

Screening tests for urine porphyrins were negative on three occasions. An Addis count revealed only an occasional W.B.C. The urine had normal levels of lead and arsenic. The electrophoretic pattern of the serum proteins was normal (October 4).

Summary

A 16-year-old white male without known trauma experienced severe pain, weakness, and atrophy of his right upper extremity, most pronounced proximally. Initially, the C.S.F. protein was elevated, but soon fell to within normal limits. Concurrently, the patient met the hæmatological and serological criteria for the diagnosis of infectious mononucleosis. He improved and was discharged after eight weeks of hospitalization. Examinations one and two months after hospitalization showed gradual subjective and objective improvement in motor and sensory functions.

Case Histories

Generation One

I.1. Male. Not afflicted with neuritis. Died at the age of 48 with "Bright's disease."

I.2. Male. Several members of the family stated that he suffered from "neuritis." The most severe attack occurred at the age of 40, when he lost the use of both arms. He experienced excruciating pain in the right upper extremity followed by severe wasting. During the acute attack he was unable to feed himself. He could not button his clothes for the remainder of his life, and he used his left hand to manipulate the right. He was able to do a little work on the farm but his right arm remained crippled.

Generation Two

II.1. Male. Not affected.

II.2. Male. At the age of 42, suffered paralysis of both upper extremities. The pain was "pitiful." The informant (II.4) stated, "I remembered it well. This attack occurred during World War I and for a long time he was unable to close his hand."

II.3. Male. Age 64. He was examined by me on October 2, 1958. He stated that he had been a "rheumatic" all his life. At the age of 6 years he had an episode of "rheumatism" involving his right shoulder and for a period of time he walked with his right arm hanging down as if he were "lopsided." At the age of 12 years he suffered an attack of pain in both shoulders associated with weakness of the upper extremities. At the age of 19 he experienced severe pain in his right hip and the entire right lower extremity. He remembered that he had to walk on his toes but could not remember whether this was because of weakness or pain. It was "months before it let up." At the age of 24 he suffered an attack of "lumbago," featured by severe pain. He was unable to stand erect and had to walk with a cane. The attack started in the winter and lasted through the spring. The following summer he was still unable to work. In 1937, at the age of approximately 44, he experienced

excruciating pain of the right upper extremity which went "into the spine." He stated that he suffered so much he wanted to die and on one occasion he passed out with pain. For nine weeks he was unable to lie down and he had to sit in a chair because of the pain in his back. One day he discovered that his right index finger was numb and paralysed. By the next night the right thumb "dropped into the palm and laid there for thirty months." Seven days following the onset of weakness in his index finger and thumb he noticed a wrist-drop, and eventually the weakness involved the arm and shoulder. His right arm "hung like a rag" for three years, and the muscles wasted.

Now he experiences occasional soreness in his muscles, and subjectively he notices occasional tingling and numbness in his right thumb and index finger dorsally and in the distal one-third of the lateral aspect of his forearm. He is still awkward with his right hand and consequently carries small change in his left pocket instead of the right. He has had no other difficulty for the past seventeen years. He is "limber as a kitten" and considers himself to be in good health and active for his age.

Examination showed absent muscle stretch reflexes in the right upper extremity. The triceps and radial reflexes were absent on the left and the biceps reflex was questionably present. The right deltoid was slightly weak, but the remaining muscle groups had surprisingly good strength. Atrophy was not obvious. He appeared healthy and was very active in his work (a service station operator).

II.4. Male. Age 78. He has pain in his upper extremities periodically but has never lost use of an extremity.

II.5. Male. Age 72. Not affected.

II.6. Female. She died at the age of 20 of an acute illness diagnosed as "spinal meningitis." One morning she awoke with a severe headache. By noon she was unconscious, and thirty-six hours later she died in coma. Examination of the C.S.F. was not done.

II.7. Female. During her lifetime she had no attacks of neuritis.

II.8. Female. Healthy all her life. Described as a strong woman, the mother of 10 children. She died at 83, and in her last years developed a tremor.

II.9. Female. She died during childbirth at the age of 20. Cause unknown.

II.10. Male. It is reported that in the last days of his life he had an episode of extreme pain involving one of his lower extremities during which he dragged the afflicted member. He died at 56 of unknown cause. No known children.

II.11. Male. It is reported that during his lifetime he had episodes of pain involving an arm and shoulder and perhaps his leg.

Generation Three

III.1. Male. Age 51. He was interviewed by telephone on October 9 and stated that he was in good health. However, during his 20's he had an episode of "rheumatic fever" and was confined to bed. This illness apparently affected his heart because he was found on numerous examinations to have a heart murmur. He had had no acute episodes of neuritis but believed that the reason he has not is that he leads a rather inactive, sedentary life. However, he notices that when he does use his right upper extremity as in bowling he may experience tingling of his fingers which usually subsides by the next morning.

III.2. Male. Age 38. He was admitted to the University Hospital on December 30, 1958. His illness began eleven weeks prior to admission when he noted pain in his right shoulder after working with his arms overhead hanging light fixtures. For a long time he had been aware that if he used his arms overhead his fingers would tingle for a few hours.

Soon after the onset of pain his right arm became weak and he developed a wrist-drop. He was then admitted to another clinic. The C.S.F. protein was found to

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be 90 mg. per cent. With this information he underwent a cervical exploration which failed to demonstrate a specific abnormality. He was placed on corticosteroid (Prednisone) therapy without improvement. Shortly before discharge, and approximately ten weeks after the onset of right-sided pain, he suddenly became hoarse and simultaneously noticed severe pain in the region of his left deltoid, followed quickly by weakness and a wrist-drop. Eight days later he was admitted here.

At the age of 6 years during an attack of scarlet fever he experienced bilateral arm pain and had to carry his arms in slings for months. He lost his voice with this attack. In 1954 he experienced pain in his right shoulder followed by a wrist-drop. He recovered completely in eight months.

When seen here he was experiencing pain so severe that it initially compromised the history and examination. The general physical examination was normal except for a healed recent laminectomy scar. The temperature was 98·6° F. and he remained afebrile. The blood pressure was 150/50, and the pulse was 88 per minute and regular.

He was obviously hoarse and on direct laryngoscopy the left vocal cord was paralysed. The deltoid, supra- and infraspinatus, biceps, triceps and brachioradialis were atrophic on the right. On a scale from 0–5, muscle power was: pectoralis 3; latissimus dorsi 0; deltoid 2; biceps 1; triceps 1; brachioradialis 1; extensors of the wrist 2; flexors of the fingers 4; interossei and lumbricals 3. The muscle stretch reflexes were absent. The C 5–6 and D 1 dermatomes showed hypæsthesia and hypalgesia. Position and vibration sensibilities were intact.

On the left the triceps and brachioradialis were slightly atrophic. Muscle power was: pectoralis 3; deltoid 1; latissimus dorsi 4; biceps 3; triceps 3; brachioradialis 1; flexors of the fingers 4; lumbricals and interossei 4; extensors of the wrist 1. The left triceps and radial reflexes were absent; the biceps reflex was normal. Sensory changes were the same as those on the right.

The muscles and nerves were not unduly tender.

Laboratory data: Examination of the urine and blood was normal except for a white count of 16,850. The serology was negative as was the urine for uroporphyrins. The fasting blood sugar was 67 mg. per cent. Total serum proteins 6·05 grammes, with 4·42 grammes albumin. The urea nitrogen was 22 mg. per cent. Heterophile titre was negative (below 1 : 56). The C.S.F. showed a total protein of 32 mg. per cent with no cells: the Kolmer was non-reactive; the colloidal gold curve was 1111110000. Serum electrophoresis was normal.

The hospital course was characterized by slow but gradual decrease in pain. He initially required 75 to 100 mg. of Demerol every four hours for control of pain. He was placed on physical therapy consisting of limited active exercises in the Hubbard tank. Strength slowly improved on the right. Fifteen days after admission he was able to elevate his right arm to the horizontal, extend the forearm, and extend the wrist to neutral but not beyond. Motor function on the left remained unchanged. At the time of discharge on January 29, 1959, fifteen weeks after the onset of pain, he was comfortable without potent analgesics. He is currently being followed in the Neurology Clinic.

III.3. Male. Age 27. He was interviewed on October 2, 1958. He stated that his attacks began in childhood. The first lasted three or four months and involved the left upper extremity; full strength returned after one year. In a second attack, at the age of 12 years, he had extreme pain for a period of three or four months during which time he lost the use of his right upper extremity. He recovered in approximately one year. The third attack occurred in 1955. He was admitted to the Caylor-Nickel Hospital, Bluffton, Indiana, April 1, 1955. Four weeks prior to admission, during a "virus chest infection" he noticed pain in his right shoulder,

scapula and forearm. A consultation report by Dr. Warren E. Hastings of Fort Wayne, Indiana, is quoted in part: "He has an acute upper brachial plexus neuritis, the cause of which is obscure. Pain and tenderness are prominent features." Other examiners found deltoid fasciculations, atrophy of the triceps, biceps, and supraspinatus, and absence of the biceps and triceps reflexes.

X-rays of the cervical spine were normal. The hæmogram and blood sugar were normal. Uroporphyrins were negative. The cerebral spinal fluid contained a total protein of 41·2 mg. per cent.

When examined on October 2, 1958, atrophy of the right pectoralis and distal symmetrical atrophy of the muscles of the forearm was apparent. The intrinsic muscles of the hand were spared. Weakness of the right deltoid and extensors of the wrists and thumbs was noted bilaterally. He was unable to fully supinate his left arm and supination was weak on the right. Questionable dysæsthesia on pin-prick was present on the anterior aspect of the right shoulder and over the atrophied pectoralis muscles. The muscle stretch reflexes were absent in the right upper extremity. The left biceps and radial reflexes were normal. Position and vibration sensibilities were intact.

III.4. Male. Apparently not affected.

III.5. Female. Age unknown. Apparently not affected.

III.6. Female. Age 64. Interviewed on October 2, 1958. In 1919 she had an episode of "severe back pain across her kidneys." She was told that "it was in the nerves." During the initial episode she received daily treatments from a chiropractor for one year. She remembered that she was unable to walk because she "couldn't handle her legs." She did not recall any wasting of the muscles. She estimated the duration of her illness from the onset until the time she was able to walk again as one to one and a half years.

As a child she had very frequent severe sore throats and her limbs frequently ached. She was operated upon in 1923 for "a growth in her throat" but was unable to recall exactly what was removed. The event that precipitated surgery was a three-month period during which she had trouble in swallowing or such difficulty getting her breath that she had to sit up most of the time.

III.7. Male. Died age 60. The informant is his second wife. As a child he suffered from "rheumatic fever" or "neuritis" in which he would have periods of pain in his arms and legs. This was reported to have been "due to dampness in the brick house."

He was married for the second time at the age of 43. His wife recalled that he suffered from "asthma" occurring in the springtime, characterized by attacks of difficulty in breathing and the feeling that the room was stuffy and close. She reported that at the age of 58 he developed pain in his neck and right arm and after a few days similar pain in the left lower extremity. This leg was weak for a few days. The arm also became weak and pain persisted for a period of six weeks. He was unable to work for three weeks. He was treated by tablets and a series of injections, as well as by chiropractic treatments. She reported an operation for a ruptured lumbar disc.

She gave the following account of her husband's terminal illness. At the age of about 60, during the winter, he developed chills, fever, and severe headache. He stayed at home for approximately one week with chills, vomiting, and nausea. After four or five days he became jaundiced. He had severe pain in his leg and because of this pain the family physician was called. Seven days after the onset of his illness he was very weak, had pain around his heart and felt as if he couldn't breathe. By this time "his kidneys had stopped up." Terminally he developed black and blue spots on his face and arms, lapsed into coma, and died January 22, 1957, four and a half weeks after hospitalization. The causes of death obtained from the death

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certificate were (1) uræmia, (2) acute tubular nephrosis, (3) leptospirosis icterohæmorrhagica.

The following information concerning his several hospitalizations was obtained from the Reid Hospital, Richmond, Indiana: On January 24, 1955, while picking up some boards he developed pain in his low back. Two days later the pain involved the left hip and leg, and after a few days it involved the knee, leg, and ankle. He then improved but developed pain in the *left shoulder*, associated with numbness of the shoulder, arm, and hand. On March 17, 1955, a lumbar myelogram showed a "definite irregularity in the opaque column at the level of the fourth lumbar intervertebral spine." On March 23 he was operated upon with "excision of herniated nucleus pulposus L 3–4."

On December 22, 1955, he was again admitted. One week prior to admission he developed malaise, bursting headache, chills and fever. The next day he vomited a great deal and the smell of food nauseated him. He complained of pain in his legs and arms. Just before admission he developed chest pain and shortness of breath. He expired on January 22, 1956.

The autopsy diagnosis was (1) Weil's disease, (2) hydrothorax, (3) atelectasis, (4) ascites, (5) severe bilateral nephrosis.

On gross examination jaundice, œdema, and subcutaneous hæmorrhages were seen. The large bowel and terminal ileum showed evidence of an acute membranous inflammatory process, with destruction of the mucosa and replacement by a purulent fibrinal exudate. The kidneys showed severe damage most prominent in the convoluted tubules compatible with an advanced nephrosis. No evidence of hepatocellular damage or acute hepatitis was found. Unfortunately, neural tissue and bone-marrow were not examined.

Titres for "Weil's disease" obtained by the Indiana State Board of Health on January 2, 1957, revealed L. icterohæmorrhagica positive to 1 : 64, L. canacola positive to 1 : 128, Pomona positive to 1 : 32. These were obtained seventeen days after the onset of his illness. Titres on January 7, 1959, twenty-two days after onset, showed positive reactions 1 : 64, 1 : 64, 1 : 56.

III.8. Male. Age 60. No difficulty. Living and well.

III.9. Female. Age 58. This patient was interviewed in August 1958. As a child she was healthy, and had no episodes of pain or "rheumatism."

Her first attack began in 1921 in the third trimester of her first pregnancy. The pain began as "rheumatism," involving the left shoulder. Soon the entire left upper extremity was so painful that she required morphine. The arm was numb and weak. She described the pain as "horrible." This episode lasted approximately two months and suddenly went away following the birth of her child. However, two weeks later she noticed pain in the right shoulder, described as being "in the bone," followed by weakness and severe pain in the right arm. This progressed to extreme weakness and wasting of the muscles. The pain lasted approximately three months. The strength in her arm gradually returned and in one year she was able to resume work.

Her second episode occurred in 1931, ten years later. She was working as a seamstress and suddenly noticed pain in the left wrist followed quickly by a wrist-drop. The pain spread to the entire left extremity and "the flesh left the shoulder." Return of function occurred in one year. Since then she has had no attacks of "neuritis." At the present time she is working as a nurse's aide in a hospital. She feels somewhat awkward in the use of her left hand and until recently has experienced mild numbness over the dorsal aspect of her left thumb and forefinger. She was examined in August 1958. She had a very slight, rhythmical, rest tremor of her right upper extremity, most pronounced distally, but without associated alteration in tone. No enlarged nerves were felt. Diminished perception of pin-prick was present in the region of the deltoid, the lateral aspect of the arm and forearm and

the first dorsal interosseus space. Touch, vibration and position sensibilities were intact. The left first dorsal interosseus was slightly atrophic. The extensors of the wrist and thumb, and possibly the infraspinatus and left biceps were weak. The triceps reflex could not be definitely elicited. The left biceps reflex was slightly brisker than the right; the radial reflexes were present and equal.

III.10. Female. Age 53. She was seen on September 5, 1958, and reported that as a child she was never ill. Her first attack occurred at the age of 19 during the second trimester of pregnancy and involved the right upper extremity. The pain was so severe that she "walked the floor." It felt as if it was "in the bone of the shoulder" and lasted one to two months. There was no weakness. The second attack occurred at the age of 23, was practically similar to the first, and also involved the right upper extremity. The third attack started one year later. This was characterized by rather sudden weakness confined to the left upper extremity. The arm "seemed dead but there was no pain." This lasted approximately one week and gradually resolved. The fourth episode occurred at the age of 43, and came on approximately two days post-partum. She experienced pain in the right shoulder which went down her arm into her fingers. The pain was very severe and she "walked the floor" for two or three weeks. Wrist-drop occurred seven days after the onset of pain. The whole arm eventually became weak. She was treated with vitamin injections for six months. During this time she gradually improved.

Her arm is now "pretty good" but there are areas of numbness. Because of the circumstances of the interview complete examination was not accomplished, but she seemed to have good symmetrical strength, the muscle stretch reflexes were present and equal and no detectable atrophy was noted. No enlarged nerves were felt.

III.11. Male. Age 49. Not affected.

III.12. Male. Age 50. Occasionally experiences tingling in his fingers as if they were asleep. No episodes of pain or weakness. He was examined by me on October 5, 1958, and no abnormalities were found. The muscle stretch reflexes were normal.

III.13. Female. Age 47. Interviewed and examined on October 5, 1958. At the age of 24 she had a febrile illness diagnosed as scarlet fever. While confined to bed she developed pain in the lumbar region which was exaggerated by movement. At times it was so severe she could not turn over in bed. The pain soon involved the left hip and the back of her left thigh. She did not recall definite weakness. The pain lasted approximately one week.

She had frequent episodes of hoarseness especially with colds. On several occasions she had been unable to speak. She recalled that I.2 was also hoarse following his attack.

During her first pregnancy, at the age of 36, she had "toxic poisoning." During the fifth months she gained 40 lb., and her "body retained water." Her blood pressure was elevated and terminally she had convulsions. The fœtus (V.44) was delivered at six months and lived only seven hours. Three weeks after delivery she noticed numbness in her left hand. One month later her left lower extremity felt numb especially at night. Her left upper extremity became weak and she was unable to raise her arm above her head. She eventually recovered.

Six months after her second pregnancy (1949) she again developed "sciatic trouble." This was of sudden onset when she was "stooped over." She had to roll in and out of bed, and was treated with five injections by a naturopath who told her that she had "a pinched nerve affecting the sciatic nerve."

III.14. Female. Age 45. No difficulty.

III.15. Male. Age 40+. Not affected. Has always been in good health.

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Generation Four

IV.1. Female. Age 22. She has eczema. She is allergic to soap and must use rubber gloves while washing dishes.

IV.2. Male. Age 19. Apparently in good health.

IV.3. Female. Age 11. Her past history is significant in that soon after birth, a neuroblastoma was found in her left eye. The right eye rapidly became involved and consequently both eyes were enucleated. She has been in good health since.

IV.4. Male. Age 16. No attacks of neuritis. Has "hay fever" during the summers.

IV.5–6. Twin females. Age 12. Not affected.

IV.7. Female. Age 8. Not affected.

IV.8. Female. Age 8. Not affected.

IV.9. Male. Age 2 months. Not affected.

IV.10. Female? No knowledge.

IV.11. Female? No knowledge.

IV.12. Female. Age unknown. Apparently not affected.

IV.13. Male. Age unknown. Apparently not affected.

IV.14. Male. Age 38. He was interviewed on October 5, 1958. In 1949 he experienced an unusual illness while serving in the armed forces. His difficulty was attributed to an injury sustained when he tripped over a log and fell. The second morning after the fall his left hip was sore. This soreness progressed to extreme pain which involved his back, and then the thigh. His foot and leg felt asleep. He had constant pain for a period of eight or nine months. He was unable to walk for two weeks because of weakness. A year passed before the strength in his leg fully returned. He was given a series of exercises to stretch his hamstrings. No myelogram was done but he did have X-rays of his back, the results of which are unknown. He has no difficulty at this time but if he gets excessively fatigued he develops a muscle soreness and aching pains in his extremities.

IV.15. Male. Age 33. Apparently has had no trouble. No children.

IV.16. Male. Age 29. It is reported that while in the Army at the age of 19 he had a severe illness "called purpura." A bone-marrow examination revealed that "there was something in his blood which ate up the iron." He "broke out all over like the measles (purpura) and was transfused with four pints of blood, and later with two pints." He was given a medical discharge.

IV.17. Female. Age 30. As a child she had frequent growing pains and sore throats.

She experienced her first severe attack at the age of 17 when she was six weeks' pregnant. The attack began with pain in her left wrist which she thought was due to a sprain. The next morning, however, the whole arm ached and by the following day she was unable to raise her arm to comb her hair or to feed herself. Her fingers, especially the index finger, were weak. A wrist-drop and marked wasting of the muscles ensued. Severe pain in this extremity lasted six weeks. Six weeks after the onset, the pain spread into the right shoulder and then down the right arm into the hand. This lasted until her pregnancy was terminated. If her arm was squeezed an electric shock radiated into her hand. Shortly after delivery, pain started in her right hip and descended to the knee. She could not remember the distribution of the pain but recalled that her leg hurt when she bent her knee or bore her weight on it. Weakness was present but not as severe as in the arms. She recovered sufficiently to take care of her baby in three months.

Her second attack occurred at 26 during her third pregnancy. Early in the pregnancy she noted pain in her left arm and hand. One or two days after the onset of pain she could not bend her fingers and "weakness came on almost with the pain." The weakness in her hand lasted during the entire pregnancy but the pain would come

and go. She said, "The pain was so bad I wanted to die." The muscles wasted during this attack. If she uses an extremity excessively she may develop transitory pain and weakness. She estimates fifteen such episodes in the past four and a half years.

Approximately two years ago she applied for a job and was found to be anæmic. ("So severe that they barely took me.") She was treated with injections and liver extract with apparent recovery. She has had poor hearing for the past eight years. Following an accident she developed transient tinnitus. She has 40 to 50 decibels of hearing loss in the right ear which is "primarily a conduction defect with a possibility of some perception loss."

She was examined by me on October 1, 1958: No apparent atrophy was present but a marked asymmetry of strength with relative weakness of the right deltoid right infraspinatus and the extensors of the right thumb was found. A very questionable decrease in perception of pin-prick over the right scapula, the palmar surface of the right thumb and index finger, and the dorsolateral aspect of the right hand including the dorsal surface of digits 1 and 2 was present. The muscle stretch reflexes, however, were normal. Vibration sense was intact. Perception of touch was patchy and inconsistent. No enlarged nerves were felt.

IV.18. The propositus. Described in detail above.

IV.19. Female. Died age 2 with pneumonia.

IV.20. Female. Age unknown. Not affected.

IV.21. Female. Age unknown. Not affected.

IV.22. Female. Age unknown. Not affected.

IV.23. Male. Age 31. Not affected.

IV.24. Male. Age 29. Not affected.

IV.25. Female. Age 16. Not affected.

IV.26. Female. Age 14. Not affected.

IV.27. Female. Age 37. Aside from being "very nervous," as are her siblings, she has had no definite episodes of "neuritis."

IV.28. Female. Age 34. Examined and interviewed on October 5, 1958. As a child she had an episode of pain in her arm which she called the "arm ache." The first definite attack occurred at the age of 19 during the first trimester of pregnancy. The initial symptom was constant pain involving the right shoulder and arm. Soon thereafter numbness was noted and then weakness. She was unable to move her right arm and hand and she used her left hand to pick it up. She was treated with injections of an unknown type and vitamin B_1. Her physician thought that her neuritis was due to poison from her tonsils since she had had frequent tonsillitis all her life. Within six months fair function had returned. Her arm is still weak and if there is heavy lifting she uses her left arm rather than her right.

In 1952 she was admitted to a hospital for excision of a benign lesion of the left breast. Her arm felt "numb" before surgery. Frank pain of the entire left upper extremity had developed by the time she had returned home from the hospital. The pain lasted approximately one month. In addition, the arm was weak. After return of function there were patchy areas of numbness especially near the wrist and thumb which lasted approximately one year.

Examination revealed no detectable atrophy and no definite sensory changes. There was an asymmetry of the muscle stretch reflexes, being graded 2 to 3+ on the right and 1 to 2+ on the left. No enlarged nerves were felt.

IV.29. Female. Age 34. Her mother reports that since childhood she has had "hyperhidrosis." Her hands and feet were persistently wet and she would frequently smear her written work at school and be reprimanded. At the present time she is being treated by a specialist for this condition which now includes a fungus infection. It is reported that she has "ulcers of the colon."

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IV.30. Female. Age 32. She was interviewed on October 5, 1958, by telephone and denied attacks of "neuritis." However, she stated that she has been allergic to many foods and has had various tests for these allergies.

During or following a "cold" seven years ago she developed difficulty in hearing. She was given a hearing test and was told that she had a 31 per cent loss in both ears "due to the nerve, the kind of deafness that cannot be helped with a hearing aid." Her hearing loss seems to be bilateral and apparently is not progressing. She is troubled only in crowded rooms when many people are talking.

IV.31. Female. Age 30. Her first unusual attack occurred at the age of 13. She was admitted to the Riley Hospital on November 10, 1941. At that time a history was obtained that three months prior to admission, after swimming, she awoke during the night exclaiming, "I think I am going crazy; my head feels numb and I can't get my breath. I'm dying!" For three months she was given electric treatments by a chiropractor. Examination at the time of admission revealed "a highly suggestible, sensitive white female of good physique, constantly moving legs, and arms, and head in a jerky, purposeless manner." On November 13 a progress note stated that the patient was "definitely psychotic" and on November 19 "that the patient was very talkative, exaggerates immensely and has a myriad of complaints." The condition was a "typical reaction of psychoneurosis." She was referred to the Child Guidance Clinic. The mother reports that the patient was treated for one year by a psychiatrist.

She was again seen at the Indiana University Medical Center on August 15, 1950, with the complaint of "neuritis with drop wrist on the right." The summer prior she had had a similar episode on the left side. This started with tingling pain, and by the next day the thumb and index finger were paralysed. This lasted a few months and gradually improved.

She gave a history of jaundice at the age of 14 which was treated with pills.

Her presenting episode began two weeks post partum at which time she noticed a constant ache in her chest which also involved the right shoulder and the right arm. She soon developed a partial right wrist-drop and was barely able to move digits 1 and 2. Although an examiner found a wrist-drop and paralysis of digits 1 and 2 the impression was "hysteria." On August 20 the patient was seen by Dr. A. T. Ross.[1] "The patient shows definite evidence of organic disease. There is some atrophy of the right supra- and infraclavicular fossæ, weakness of the right triceps, severe weakness and atrophy of the right brachioradialis, atrophy and flabbiness of the right forearm, paralysis of the extensors of the wrist and proximal phalanges, weakness of supinators and pronators of the right forearm, and weakness of flexors of all digits. The ulnar group performs well. On the left the deltoid has less substance. Neither shoulder can be abducted as well as it should. Could not elicit either triceps reflex. The radial reflex is absent on the right and the right triceps reflex not as active as the left. There is no definite hypalgesia except over the right first dorsal interosseous. Impression: Right brachial neuritis mainly radial and to some extent median. She complains of pain in the left arm and this, with some deltoid atrophy, suggests neuritis also on the left." X-rays of the cervical and dorsal spine were normal.

IV.32. Female. Age 35. Not affected.

IV.33. Male. Age 33. Not affected.

IV.34. Male. Age 30. At the age of 18 he had an episode of dysphagia which cleared spontaneously.

IV.35. Female. Age 23. Not affected.

IV.36. Female. Age 23. Reported to be currently affected with neuritis

[1]Chairman, Department of Neurology, Indiana University Medical Center.

associated with a recent pregnancy. The following detailed report was provided through the courtesy of the United States Naval Hospital, Memphis, Tennessee, T. E. Hair, Jr., Lt. M.C., U.S.N.R., attending:

"This 23-year-old white married female was admitted to this facility on 23.2.58 for spontaneous delivery of a full-term infant. The patient was gravida III. Immediate post-partum course was uneventful. Approximately five days after delivery and two days after returning home, the patient noted onset of pain in the distribution of the left radial nerve with an associated wrist-drop. She was seen in the clinic where physiotherapy and vitamin B_{12} injections were begun. However, over the following two weeks, improvement failed to occur and a repeat examination revealed partial involvement of the radial and median nerves of the left arm with weakness of the intrinsic muscles supplied by these nerves in the hand, and partial wrist-drop. However, she was able to extend the wrist to the ulnar side. The brachioradialis muscle functioned strongly. There was hypalgesia of the tip of the thumb and second and third fingers of the left hand and local tenderness was noted in the mid upper arm but no evidence of a lesion or bony deformity could be detected. At this time a complete physical examination failed to reveal any other abnormalities. There was no family history of diabetes. The patient had no other associated symptoms.

White count showed 5,400 cells with 44 neutrophils, 51 lymphocytes, 2 monocytes, 1 eosinophil, 1 band, and 1 basophil. Hæmoglobin was 14 and sedimentation rate 11. Urine was negative for porphyrins. B.U.N. was 17 and fasting blood sugar 106.

The patient was continued on physiotherapy including electrical stimulation. A lumbar puncture was performed on 24.7.58 which showed an opening pressure of 120. The fluid was clear and contained a total protein of 27·9 mg. per cent. A Queckenstedt with the head in a flexed position was negative. The patient continued to notice discomfort in the entire left arm and failed to improve on physical therapy. Around August 1, the patient began noting some discomfort in the neck and right shoulder and some reference of pain to the right shoulder blade and a tendency of the shoulder blade to be prominent. Examination revealed winging of the right scapula; otherwise, the picture was the same.

On August 14 she was admitted for a myelogram. The general physical examination was again normal. The extremities revealed the muscles of the left arm to be quite flabby with no obvious atrophy but some swelling about the left wrist. A neurological examination revealed total weakness of the left arm. The deep tendon reflexes were all present except for the left triceps. Hypæsthesia of the entire left arm up the shoulder in somewhat glove-like distribution was present. The cranial nerves were normal. No sensory defect could be noted. Accessory clinical findings at that time revealed a urinalysis to be negative, white count was 5,400 on two occasions with normal differential. Sedimentation rate was 10.

Because of the intense pain, it was deemed necessary to place the patient on Demerol every four hours and on the night of admission she was begun on Cortisone, and by the following morning the pain had been greatly reduced. The Cortisone was continued for only a period of two days after which it was discontinued. L.E. preparations have been negative.

On August 16 a myelogram was performed which was negative. Sugar determination on the fluid removed was 81 mg. per cent and total protein 22·8 mg. per cent. Skull series and films of the entire spinal column have been negative. Following the myelogram, the patient was discharged on thiamine chloride 50 mg. three times a day and was instructed to continue physiotherapy on an out-patient basis. A subsequent report received January 29, 1959, indicated that the patient was markedly improved. She reported a general hypæsthesia of the entire left arm

most prominent distally. The left triceps reflex was absent. A repeat glucose tolerance test was normal.

IV.37. Female. Age 23. Two years ago during a pregnancy she developed severe pain and weakness in her right arm which subsided in three to four months.

IV.38. Male. Age 22. During the winter when he was 18 he had pain and weakness of one shoulder which improved. Apparently has had no difficulty since.

IV.39. Female. Age 20. Not affected.

IV.40. Male. Age 14. Not affected.

IV.41. Female. Age 10. Not affected.

IV.42. Male. Age 20. In good health.

IV.43. Male. Age 18. In good health.

IV.44. Female. Age 13. In good health.

IV.45. Male. Age 11. In good health.

IV.46. Male. Age 7. In good health.

IV.47. Male. Died seven hours following birth. Premature. Mother eclamptic.

IV.48. Male. Age 9. At the age of 6 years a heart murmur was noted. The next summer the child complained of easy fatigability and wanted to go to bed in the morning. His right leg ached and felt numb like it was asleep. After a month he was taken to his family physician who did a "blood test for rheumatic fever which was negative," and put the child to bed. This episode of leg ache lasted approximately two months.

IV.49. Male. Age 9. He is reported to have severe attacks of asthma, in which he must sit up to breathe. Other than this, he is apparently well.

IV.50. Female. Age 4. No difficulty.

IV.51. Male. Age unknown. Allegedly in good health.

Generation Five

V.1. Female? No knowledge.

V.2. Female? No knowledge.

V.3. Female. Age 17. Has had "hives due to nerves."

V.4. Female. Age 15. Not affected.

V.5. Female. Age 14. Not affected.

V.6. Male. Age 6. Not affected.

V.7. Male. Age 3. Not affected.

V.8. Male. Age 12. Described as being very healthy.

V.9. Male. Age 8. He has frequent tonsillitis and sore throats. He is allergic to penicillin and sulpha drugs which cause "welts and hives."

At 4 years of age during an attack of tonsillitis he awoke at night with pain in his right arm. Soon thereafter there was weakness of the right upper extremity and a profound wrist-drop. He was treated with vitamin B_1 and B_{12} without benefit. The extremity became progressively weaker and the muscles wasted away. The index finger was the most severely involved. He tended to carry his forearm across his chest with the hand hanging down. He was treated by physical therapy, exercises, and whirlpool, but it took him over a year to recover. Severe pain lasted two months. At 6 years he had his tonsils removed and since then he has been a healthy child. Prior to this "he was continually sick." Before the tonsillectomy a prolonged clotting time was found. He was treated successfully with vitamin K.

He was examined on October 1, 1958. No enlarged nerves were felt. The patient had good symmetrical strength of the shoulder girdle, biceps, brachialis, triceps, supinators, and pronators, flexors, and extensors of the wrist and the intrinsic muscles of the hand. No sensory changes were noted; the cranial nerves were intact. An asymmetry of the muscle stretch reflexes was found. The biceps and triceps reflexes were absent on the right and the radial reflex was diminished as compared to the left.

V.10. Male. Age 4. In January 1958, at the age of 3 years, he developed gross hæmaturia. He had had a sore throat for three weeks prior to this and was treated with Achromycin. A diagnosis of "Bright's disease" was made. The hæmaturia lasted approximately two months. He became pale and lost weight. The blood pressure was unknown. Concerning this illness, a copy of a consultation by Dr. Paul J. Fouts, who saw the patient February 21, 1958, was obtained:

"It was noted that the patient apparently had sudden onset of gross hæmaturia and œdema of hands and face on January 3, 1958. The mother states that he had a half brother (V.9) who is a bleeder. The brother apparently was found to have a prolonged bleeding time one year ago and bled slightly following tonsillectomy. Examination revealed a bleeding time of 1½ minutes, coagulation time (Lea and White) 10½ minutes, clot retraction was normal. The blood cell count was 4·58 million, hæmoglobin 10·6 grammes, white blood count 5,900, hæmatocrit 34, sedimentation rate 0 millimetre per hour corrected. Differential: polys. 20, lymphocytes 68, mono. 8 per cent, eosin. 2 per cent, baso. 2 per cent, platelet 549,600. Red blood cells were hyperchromic. Urine showed traces of albumin, many white blood cells and red blood cells and numerous granular hyalin cellular casts. This boy evidently still has active nephritis and I do not believe that he has hæmorrhagic tendencies. He should be started on iron."

V.11. Male. Age unknown. Not affected.

V.12. Female. Age unknown. Not affected.

V.13. Female. Age unknown ("small"). Not affected.

V.14. Female. Age unknown ("small"). Not affected.

V.15. Male. Age unknown ("small"). Not affected.

V.16. Male. Age unknown. Not affected.

V.17. Male. Age unknown. Not affected.

V.18. Male. Age 13. He has a profound congenital amblyopia of the left eye inherited from his father. The father, unrelated to this family tree, is also effected.

V.19. Female. Age 11. Sister of V.18. She also has a congenital amblyopia of the left eye.

V.20. Female. Age 16. In the last two years she has had three episodes of pain in the right shoulder and arm which lasts two or three days. There has been no definite weakness. Otherwise she has been in good health.

V.21. Female. Age 14. No difficulty.

V.22. Male. Age 11. He has had two or three episodes of tonsillitis every year since birth.

V.23. Male. Age 7. Apparently not affected.

V.24. Female. Age 9. Allegedly has "eczema."

V.25. Female. Age 7. In good health.

V.26. Male. Age 3. In good health.

V.27. Male. Age 8. Not affected.

V.28. Male. Age 5. Not affected.

V.29. Female. Age 11. Not affected.

V.30. Female. Age 9. Not affected.

V.31. Male. Age 3. Said to be anæmic and needs iron.

V.32. Male. Age 1. Not affected.

V.33. Female. Age 8. Not affected.

V.34. Male. Age 5. Two epileptic attacks.

V.35. Newborn.

V.36. Male. Age 2. Normal.

V.37. Male. Age 2. Normal.

V.38. Male. Age 1. Normal.

V.39. Female. Age unknown. Normal.

V.40. Female. Age unknown. Normal.

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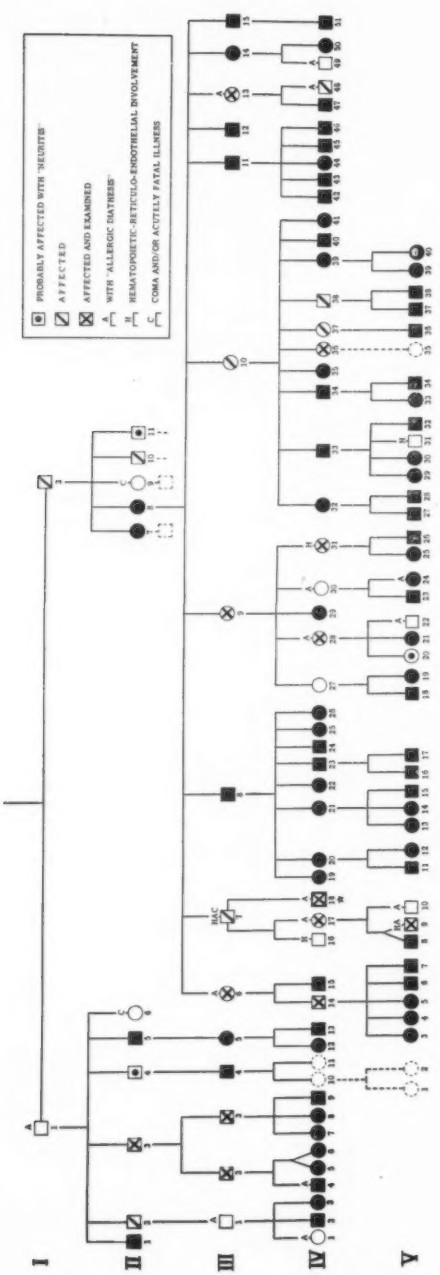

FAMILY WITH HEREDOFAMILIAL MONONEURITIS MULTIPLEX

Discussion

Attacks of Neuritis—Male (Table I)

In the five generations, a total of 60 males is recorded; 14 of the 60, or 23 per cent of the males have had attacks of neuritis. Generations IV and V are still too young to permit full expression of the neuritis.

Table I.—Attacks of Neuritis—Male

Case	*Right upper*	*Left upper*	*Right lower*	*Left lower*
I.2	1	1		
II.2	1	1		
II.3	3	1	1	
II.10			*	*
III.2	2 bilateral	2		
	1			
III.3	2	1		
III.7	1	1		1 disc?
IV.14				1 disc?
IV.18	1	?1		
IV.38	*	*		
IV.48			1	
V.9	1			
Total	13	7	2	2

*Side unknown.

In generation I, I.1 died of Bright's disease at the age of 48, and I.2 suffered a severe neuritis attack with permanent disability.

The average known age of the second generation is 70 years. Of the 7 males in this generation, at least 3 had definite attacks and 1 (II.4) had periodic pains without obvious paralysis. II.11 may have been affected.

The third generation has an average age of 51 years. Of 9 males, 3 had definite attacks of neuritis, and 6 are unaffected. Case III.2 had three separate attacks, two being bilateral.

The fourth generation averages 21 years; of 21 males 4 have been affected so far.

The fifth generation averages only nine years. Only one (V.9) has been affected so far. He represents the youngest involved, having suffered an attack at the age of 4 years, although III.2 had disabling bilateral arm pain at the age of 6 years.

Table I lists the site of involvement, and the number of attacks experienced. In the males the right arm is affected twice as often as the left (13 : 7). The reason for this is not known, but perhaps it is related to use. Many are labourers and farmers, and, in fact, 3 members (III.1, III.2, III.12) report transient tingling in their fingers if the extremity is used excessively. III.2 attributes the onset of his recent severe attack

to working with his arms overhead for a prolonged time. This discrepancy between right and left sided involvement is not as apparent in the affected females, or in either sex when the lower extremities are involved.

Attacks of Neuritis—Female: with Pregnancy (Table II)

The association of single or recurrent attacks of neuritis with pregnancy is a striking feature. If the fifth generation is deleted because the average age (9 years) is far below the child-bearing age, 8 members, of a total of 37 females in the second, third, and fourth generations, or 22 per cent, have had attacks associated with pregnancy. Unlike the males' attacks, these attacks during pregnancy have approached equal lateralization. Seven attacks involved the right upper; five attacks, the left upper; one, the right lower; and one, the left lower.

TABLE II.—ATTACKS OF NEURITIS—FEMALE WITH PREGNANCY

Case	*Right upper*	*Left upper*	*Right lower*	*Left lower*
III.9	1	1		
III.10	2			
III.13		1*		1
IV.17		2	1	
IV.28	1			
IV.31	1	1		
IV.36	1			
IV.37	1			
Total 8	7	5	1	1

*Three weeks post partum.

Attacks of Neuritis—Female: Not Associated with Pregnancy (Table III)

8 female members have had attacks not associated with pregnancy. However, of these 8, only 2 (III.6 and V.20) have not had additional attacks during a pregnancy. III.6, unaffected during pregnancy, had

TABLE III.—ATTACKS OF NEURITIS—FEMALE NOT ASSOCIATED WITH PREGNANCY

Case	*Right upper*	*Left upper*	*Right lower*	*Left lower*
III.6			1	1
III.9		1		
III.10	1	1		
III.13				2 disc?
IV.17	1*			
IV.28		1		
IV.31		1		
V.20	1			
Total 8	3	4	1	3

*Side unknown.

involvement of her lower extremities only. V.20 is only 16 years of age and unmarried. The complete neuritic syndrome may be expected with her first pregnancy.

Neuritis versus Protruded Disc

When the upper extremity has been involved, and the cases well documented (III.2, III.3, IV.18, IV.31, IV.36, V.9), an explanation of the process by mechanical pressure from a protruded disc is not tenable. The onset, symptoms, wide distribution, and course exclude this possibility. 4 patients (III.3, IV.18, IV.31, IV.36) had negative cervical X-rays, and 2 (IV.18 and IV.36) negative cervical myelograms. III.3 underwent, at another clinic, a cervical exploration which disclosed no abnormalities.

When the lower extremities have been affected, the differential diagnosis between a simple mechanical lesion (disc) and neuritis is difficult on clinical grounds alone.

5 males and 3 females have experienced episodes of back and leg pain (Tables I, II, and III). II.3 had four recurrent attacks of brachial neuritis. At the age of 19 he experienced an episode of right hip and leg pain which lasted "for months," and again at the age of 24 he suffered an attack of "lumbago," which incapacitated him for eight months. If it is assumed that the current attacks in the arms were not due to root compression by multiple discs, it is valid to speculate that the attacks of leg pain and lumbago may have been caused by a process other than mechanical, one similar in ætiology to that involving the nerves of the upper extremity.

Case III.7 presents documented evidence of intervertebral disc disease (lumbar myelography and surgery). However, the description of his successive distribution of pain as given by the wife is interesting. It started in his right neck and arm, and after a few days involved the left lower extremity. The hospital records describe concomitant pain and numbness of the left upper extremity. At the onset of his terminal illness, the complaint that summoned the physician was severe pain in the left hip and leg, which may have been a recurrent disc protrusion or a neuritis associated with an overwhelming febrile illness.

III.13 developed leg pain at the age of 24 during a febrile illness diagnosed as scarlet fever. A second episode occurred fourteen years later. It was of sudden onset and indistinguishable from disc disease with protrusion and compression.

IV.14, while in the army, experienced severe left leg pain attributed to an injury. The pain was associated with weakness and numbness of his leg and foot. Weakness lasted one year. X-rays of the back were done, but a myelogram was not performed.

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IV.17 experienced three separate attacks of brachial neuritis. Concurrent with one of these attacks, she developed right hip and leg pain, associated with pregnancy.

IV.48 at the age of 6 years, during a vague illness diagnosed as rheumatic fever, developed numbness and aching pain in his right leg which lasted two months. The patient's age and the mode of onset would seem to rule against root compression from a protruded lumbar disc.

Possible Cranial Nerve and Autonomic Involvement (Table IV)

Hoarseness accompanied neuritis in 5 cases. 3 of these are well documented. IV.28 became hoarse during her first attack of brachial neuritis. IV.18, the propositus, had definite right recurrent laryngeal nerve involvement with paralysis of the vocal cord demonstrated by indirect laryngoscopy. III.2 became hoarse with his first attack at the age of 6 years. Paralysis of the left vocal cord occurred during the third attack when the neuritis advanced to involve the left brachial plexus. This was demonstrated by direct laryngoscopy.

TABLE IV.—POSSIBLE CRANIAL NERVE OR AUTONOMIC INVOLVEMENT

Case	*Type of involvement*
I.2	Hoarse
III.2	Became hoarse with first and third attacks
III.6	Three-month period of difficulty in swallowing—age 29
III.13	Frequent episodes of "hoarseness"
IV.17	Possible right VIII (partial)
IV.18*	Right Horner's—right recurrent laryngeal
IV.28	Became hoarse with first attack—recurrent laryngeal—age 19
IV.29	Hyperhidrosis since childhood
IV.30	Bilateral partial nerve deafness (31 per cent)
IV.31	Difficulty in swallowing—three months—age 13
IV.34	Episode of difficulty in swallowing—age 18

*The propositus.

3 members had prolonged episodes of difficulty in breathing or swallowing. IV.31 specifically recalled her trouble at the age of 13 as difficulty in swallowing. The complaint was considered hysterical, a frequent "diagnosis" in this family. She was treated by a psychiatrist for one year. Nine years later she had a severe attack of brachial neuritis.

2 cases of partial nerve deafness are recorded. IV.30 discovered impaired hearing following an upper respiratory infection. This has persisted, but has not progressed. IV.17 has a combined hearing loss.

IV.29 has experienced excessive sweating since age 7. She is currently being treated by a psychiatrist for this complaint.

"Allergic Diathesis" (Table V)

In an incomplete survey, 17 individuals, or 14 per cent, were found to have the various reactions listed in Table V. The term "allergic diathesis" is chosen with misgiving. It is not intended to indicate real knowledge of the basic mechanism.

TABLE V.—"ALLERGIC DIATHESIS"

Allergic, specific agents	"Rheumatic fever"
IV.1 soap	III.1
IV.30 "many foods"	IV.18
V.9 sulfa and penicillin	IV.48
Asthma	Frequent sore throats—scarlet fever
III.7	III.6
IV.49	III.13
Hay fever	IV.17
IV.4	IV.18
"Bright's disease"	IV.28
I.1	V.9
V.10	V.22
Eczema	Toxæmia pregnancy
IV.1	III.13
V.24	
"Growing pains"	
III.6 (neuritis?)	
III.7 (neuritis?)	
IV.17	
IV.28	

4 patients had vague aching pains in their extremities during childhood. "Growing pains" is the expression used by the informants. These episodes of discomfort may actually represent neuritic attacks which failed to develop into the complete atrophic and paretic picture characteristic of the adults. One member (V.9) did develop the complete syndrome at the age of 4 years. III.2 at the age of 6 developed painful upper extremities which he had to carry in slings for several weeks.

The remainder of Table V is self-explanatory.

Hæmatopoietic—Reticulo-endothelial System (Table VI)

This system has been involved in 5 members, 4 males, and 1 female (IV.31). IV.16 developed purpura, requiring transfusions at the age of 19. III.7 suffered an acute febrile terminal illness diagnosed, perhaps erroneously, as Weil's disease. An autopsy was performed and is reported under the case history. Titres obtained seventeen days after the onset of the illness were 1 : 64; 1 : 64; 1 : 16. Unfortunately no neural tissue was examined.

3 members in apparent good health developed acute terminal illnesses. II.6 died in coma at the age of 20. II.9 died of unknown cause during child-birth, and III.7 of Weil's disease.

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TABLE VI.—HÆMATOPOIETIC—RETICULO-ENDOTHELIAL

Case	*Type of involvement*
III.7	Purpura with "Weil's disease"—jaundice
IV.16	Purpura—age 19
IV.31	"Yellow jaundice"—age 14
V.9	Prolonged clotting time
V.31	Anæmic—"needs iron"

COMA AND/OR ACUTE DEATH

Case	*Type of involvement*
II.6	"Spinal meningitis"
II.9	In childbirth—cause?
III.7	"Weil's disease"

Alleged Precipitating Causes other than Pregnancy (*Table VII*)

4 members (III.2, III.3, III.13, V.9) gave a history of a febrile illness as the precipitating cause. IV.18, the propositus, had hæmatological and serological evidence sufficient for the diagnosis of infectious mononucleosis concomitant with his initial right brachial neuritis.

TABLE VII.—PRECIPITATING CAUSES OTHER THAN PREGNANCY

Case	*Type of involvement*
III.2	Scarlet fever (first attack)—possible excessive use (third)
III.3	Third attack—"virus in chest"
III.13	Febrile illness—"scarlet fever"
IV.14	Possible trauma
IV.18	Infectious mononucleosis
IV.30	Bilateral persistent nerve deafness following "a cold"
V.9	Tonsillitis

IV.30 relates the onset of bilateral nerve deafness to "cold." III.2 incriminates excessive use of his arms overhead as the cause of his third attack, which started on the right. Excessive use, however, could hardly be the cause of the left brachial involvement which began eight weeks later. IV.14 considered trauma to be the precipitating cause of his only attack of right hip and leg pain and weakness. III.1 experiences tingling of his fingers and IV.17 pain and weakness after excessive use.

Cause and genetic determination.—At what level the basic defect is operating remains unknown. The neural involvement, however, is clearly genetically determined. The defect appears to be transmitted by an autosomal dominant gene which has a high degree of penetrance. If generations IV and V are excluded because the members are still too young to permit full expression of the trait, generations I, II, and III show a dominant transmission with a penetrance of 85 per cent. Only 2 individuals (I.1 and II.8) carried the gene and failed to show the trait.

Because of the close similarity of the neural involvement in this family to serum neuritis, which has an allergic basis, and the fact that the attacks may be precipitated by such superficially dissimilar stresses as pregnancy, trauma, excessive use, and febrile illnesses, I propose that through a genetically determined defect, the peripheral nerves in affected members

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may be the prime target tissue for hyperergic reactions. Other tissues may at times be involved perhaps because of independent or closely related genetic defects. Many factors, both external and internal, would appear to be operating in the final neural expression of the defect in a given affected individual. In this regard, a quotation from a recent article by Snyder (1959) seems appropriate: "Each individual has a unique assembly of genes and will have his own mode of reaction to disease whether it be presented through trauma, stress or malnutrition, or wholly from within through biochemical error."

Summary

(1) A family, consisting of 119 individuals representing 5 generations has a strong predilection for the occurrence of single or recurrent attacks of neuritis.

(2) 23 per cent of the males and 22 per cent of the females of child-bearing age have so far been affected.

(3) The neuritis is most frequently brachial in location, but cranial nerves, as well as single or multiple peripheral nerves have been involved. The peripheral neuritis is characterized by excruciating pain, weakness, atrophy and sensory loss. Functional recovery after many months is the rule; however, long-standing residual deficits are seen. Attacks associated with pregnancy are characteristic.

(4) The basic defect is transmitted by an autosomal dominant gene with a high degree of penetrance. The neural involvement closely resembles serum neuritis and the fundamental defect may be genetically determined susceptibility of the peripheral neural tissue to hyperergic reactions.

Acknowledgments

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BASILAR IMPRESSION AND OSTEOGENESIS IMPERFECTA IN A FAMILY

BY

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THE familial occurrence of Primary Basilar Impression has been studied by Bull *et al.* (1955). They found 11 abnormal relatives in the families of 7 of their 20 affected patients and they considered the mode of inheritance to be an example of Mendelian dominance with incomplete penetrance. Basilar impression may also occur in other types of skeletal disease, especially in Paget's disease (Bull, 1946) but also in osteogenesis imperfecta, hyperparathyroidism and osteomalacia (Bull, 1951).

The family which is reported in this paper afforded an opportunity of studying the relationship between basilar impression and osteogenesis imperfecta and their clinical effects.

The family pedigree is shown in fig. 1. The parents were not related

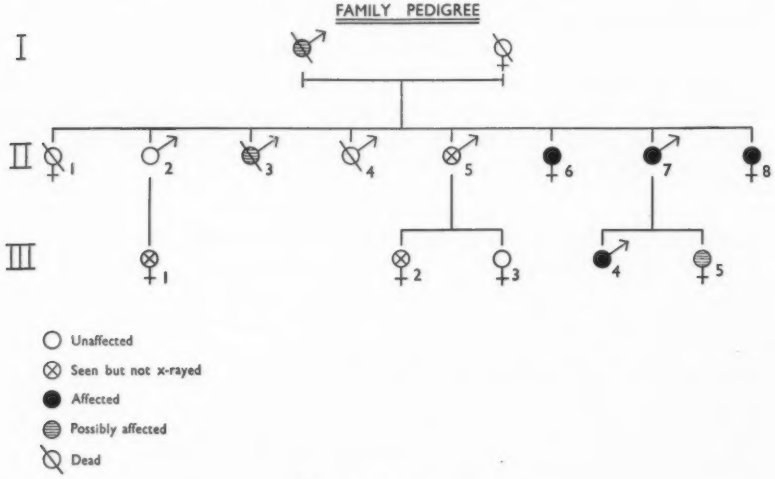

FIG. 1.—Pedigree.

to one another. The father died aged 47 years. He was said to have been short in stature and to have had a short neck. There was a vague statement from a member of the family that he had deformities. The mother was normally proportioned, and she died aged 42 years from an unknown cause. The eldest sister (II 1) was said to have died aged 24 years in childbirth, the baby (first child) being stillborn. A brother (II 3) died aged 26 years. He was short in stature and was never able to go to work. A brother (II 4) died aged 2 years from unknown cause. Cases 1 and 2 (II 7 and II 8) and the other surviving siblings, two brothers and a sister, were seen and examined clinically. Both brothers (II 2 and II 5) were normal in stature and had no abnormal physical signs. Their serum calcium, phosphorus and alkaline phosphatase were within normal limits. The skull X-ray appearances in one brother (II 2) were normal but this examination could not be done in the other brother. The sister (II 6) was of short stature and presented abnormal neurological signs and her case is reported in more detail below. The 5 children of the siblings were seen but blood and X-ray examinations were refused in III 1 and III 2. III 3 aged 16 was normal on clinical examination and the X-ray appearances of her skull were normal. Her serum calcium and phosphorus were 11·0 and 4·2 mg. per cent respectively. The alkaline phosphatase was 21 K.A. units which is a high normal value for her age. Both children of Case 1 (R. G.) (III 4 and III 5) showed slight radiological abnormality and their cases are reported below.

Case Reports

Case 1.—R. G., male, aged 36 years. (II 7) N.H. No. 6557. In October 1947, when aged 26 years, he was first admitted to the National Hospital, Queen Square, under the care of Dr. J. Purdon Martin. The presenting symptoms were stiffness in the jaw muscles with paræsthesiæ in the face for two to three months and of severe headaches for two to three weeks.

He said that he had had a curvature of the spine and a broad skull for as long as he could remember. As a boy he often found difficulty in regaining his feet if he had been pushed over. He had always been short in stature but as a boy had not complained of pain or aching in the limbs. He was an above-average scholar and played games at school without sustaining any bony injury. When aged 15 years he fell off his bicycle and found that he could not move his legs for some time. Regaining his feet he walked with difficulty. However, because of pain and the persistence of the walking difficulty, he attended a local hospital where X-ray examination revealed three fractures in the pelvis. After recovery he returned to work as a milk boy, cycling several miles a day, and when aged 17 years he again had an accident and this time was unconscious for an hour. X-ray of the skull showed a fracture and for about a week he had a discharge of cerebrospinal fluid from the right ear. He has been deaf in the right ear since then and he complained of tinnitus in this ear for the following three years. He returned to the milk round but at the age of 20 years he once more fell off his bicycle, and he was treated in the hospital for a stiff and painful left hip. Determined to forsake the hazards of cycling he took up employment as a telephonist and he had few complaints. He did, however, notice during the years before his first admission that he would have severe sharp, but momentary, pain in the

back of the head on coughing, laughing heartily and straining; he soon learned to avoid these precipitating factors.

About three months before his admission he began to complain of sudden attacks in which the lower jaw would become fixed in a partially open position, and he would be unable to open or close it. He described it as a cramp in the muscles which would last a few seconds. Some weeks after the onset of this symptom there was associated with each attack a sensation of pins and needles beginning in the right side of the skin of the lower jaw and spreading rapidly up the right side of the face to the forehead and into the right side of the tongue. At the same time he would become aware of a feeling of deadness around the lips. While he had the pins and needles, he noticed impaired sensation in the right side of the face if he were to touch it with his finger. These attacks would last about a minute and were often precipitated by coughing and straining. In the two to three weeks before his admission there was associated blurring of vision and diplopia and sharp occipital headache. Occipital headache also occurred alone in spasms during this period and became increasingly severe.

On examination he was 64 in. tall, short necked with a prominent external occipital protuberance. The head showed pronounced temporal bulging. He had severe dorsolumbar kyphoscoliosis. There was a marked transverse groove in the abdomen with the ribs reaching the iliac crests indicating loss of stature. The pelvis was deformed and the right leg was about 1 in. shorter than the left. There was bilateral papillœdema with a few streaky hæmorrhages. Visual acuity was 6/6 on both sides. There was slight impairment of the right corneal reflex and of sensation in the distribution of the right fifth cranial nerve. He had severe right conduction deafness. The rest of the cranial nerves were normal. Tone was slightly increased in the legs. He had slight terminal intention tremor, particularly in the left hand, on doing the finger-nose test. Power was normal in all limbs. The tendon reflexes were brisk and the right plantar response extensor and the left indefinite. Sensation was intact apart from slight impairment of vibration sense in the legs. The clinical diagnosis with regard to his neurological condition was of basilar impression with hydrocephalus.

X-ray examination of the skull showed a gross degree of basilar impression, the angle between the hard palate and the atlas (Bull's angle) being 48 degrees (fig. 2, Plate XXI). Wormian bones were present in the skull. The X-ray appearances of the dorsal and lumbar spine indicated some lack of demineralization of bone, and the X-ray films of the pelvis showed flattening and a gross degree of protrusio acetabuli on the right side.

On 7.11.47 Mr. Jackson performed a posterior fossa decompression. The occipital bone was found to be extremely thin. A marked cerebellar cone was noted with the cerebellar tonsils as low as the level of the axis vertebra.

The immediate post-operative course was stormy because of what appeared to be a central disturbance of respiration, but after a few days recovery proceeded satisfactorily. On discharge on 2.1.48 the papillœdema had subsided. The patient had no headaches and indeed was symptom free.

He remained in satisfactory health and at work until January 13, 1956, when he slipped off a ladder and fell about 10 ft. on to his back. He complained of severe pain in the pelvis and in both hips, and X-ray examination revealed the presence of a further fracture. He was admitted to another hospital and treated in a Thomas' splint for some weeks, but the pain returned as soon as the splint was removed. Thereafter he walked with a limp and had severe and continuous pain, worse on exercise in both hips and knees. There had been no difficulty in micturition.

He was readmitted to the National Hospital, Queen Square, on July 2, 1956, for further study.

On examination his height was now 60½ in. Span 69 in., crown to pubis 26 in. This indicated increasing loss of height. There was 1½ in. of shortening in the right leg.

FIG. 2.—X-ray of the skull in Case 1, showing the gross degree of basilar impression.

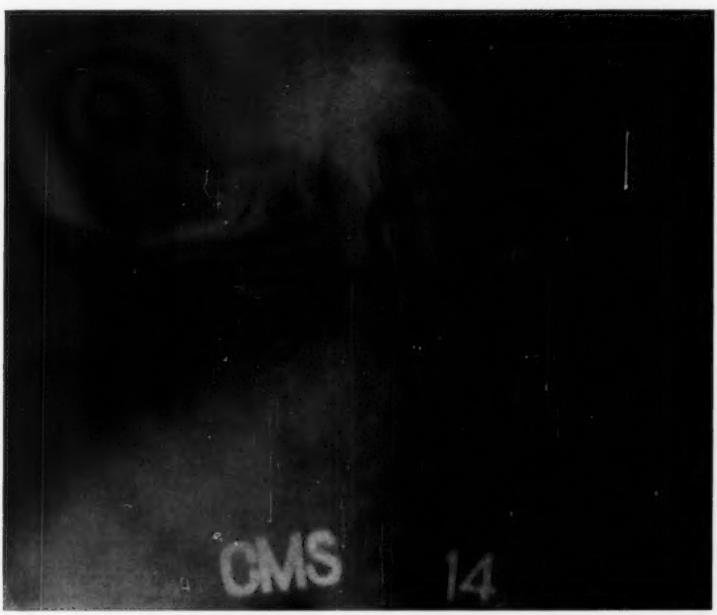

FIG. 4.—A lateral tomogram of the skull in Case 2, showing the very gross degree of basilar impression.

To illustrate article by L. J. Hurwitz and R. R. McSwiney.

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A

B

FIG. 3.—X-ray of the pelvis in Case 1: A, 1953 showing the gross protrusio acetabuli on the right. B, 1956—there is protrusio acetabuli on the left as well. The head of the femur is pushed through into the pelvis.

To illustrate article by L. J. Hurwitz and R. R. McSwiney.

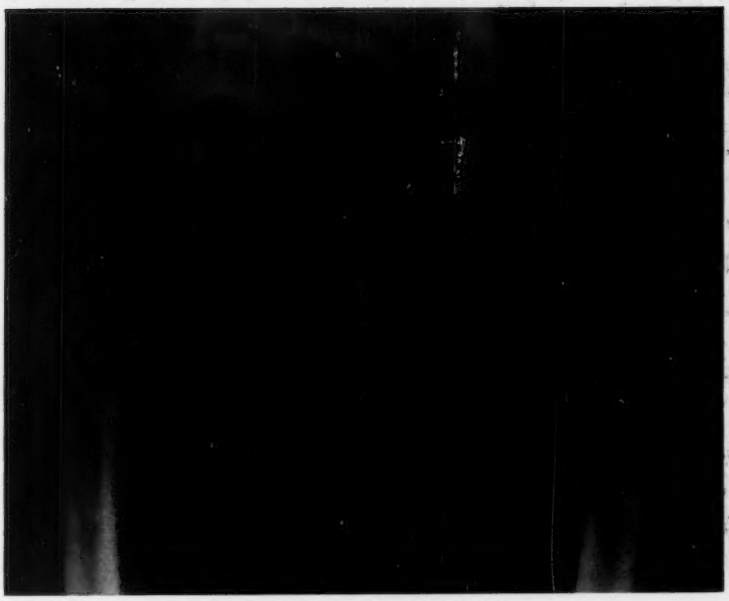

FIG. 5.—The pelvis in Case 2 showing a slight protrusio acetabuli.

FIG. 6.—A photograph at operation in Case 2 showing a gross degree of intramedullary cavitation of the cervical cord.

To illustrate article by L. J. Hurwitz and R. R. McSwiney.

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FIG. 7.—This shows the striking resemblance between the sisters and the marked degree of prognathism.

To illustrate article by L. J. Hurwitz and R. R. McSwiney.

FIG. 8.—A lateral tomogram of the skull in Case 3, showing a milder but definite degree of basilar impression.

To illustrate article by L. J. Hurwitz and R. R. McSwiney.

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The posterior fossa decompression was flat. Visual acuity was again 6/6, but the discs were uniformly pale with hazy, ill-defined margins indicating some degree of consecutive optic atrophy. There was no evidence of papillœdema. The fields of vision were full. The pupillary responses were normal. The right corneal reflex was diminished but sensation was unimpaired in the face. The rest of the cranial nerves were normal. Tone was normal in the arms and slightly increased in the legs. The tendon reflexes, including the jaw-jerk, were all increased and both plantar reflexes were extensor in type. The power in the limbs was normal. Vibration sense was a little diminished in the legs and there was slight impairment of postural sensation in the toes. Sensation was otherwise intact. Movement at both hips, but especially the left, produced pain and there was very marked limitation of rotation at both hip-joints and slight limitation of other hip movements. The patient's blood pressure was 105/60 and his cardiovascular system seemed normal. He was edentulous.

Investigations.—Blood hæmoglobin 92 per cent. White blood corpuscles 7,750 with a normal differential count. Blood group B Rh positive. Glucose tolerance test normal. W.R. negative.

The specific gravity of the urine was 1020 and there was no albumin or sugar or abnormal casts. Urinary 17 ketosteroids 11·2 mg./24 hours. Urinary amino-acid nitrogen 445 mg./24 hours. Paper chromatography showed a normal pattern of urinary amino-acid excretion.

Fat balance over six-day period showed 98·3 per cent absorption.

X-ray examination of the pelvis showed gross protrusio acetabuli on both sides and comparison with the old films showed that this had become more severe since 1947. The head of the left femur had virtually broken through the acetabulum (fig. 3). X-rays of the rest of the skeleton showed no obvious fractures or Looser's zones, but the bones were abnormally thin and there was bowing of the long bones, showing severe calcium deficiency of bone.

Dr. M. D. Milne kindly admitted this patient to the Metabolic Ward at Hammersmith Hospital on 24.1.57. The results of estimations of the calcium, phosphorus and nitrogen balances are given in Table I. The calcium studies showed a normal absorption of calcium from the gut and normal excretion in the urine. The serum

TABLE I.—CALCIUM, PHOSPHORUS AND NITROGEN BALANCE ESTIMATIONS ON R. G. (II 7) BEFORE AND AFTER CALCIFEROL

Amounts per day		*Period* 1	*Period* 2 *Calciferol*	*Period* 3 150,000 *units*	*Period* 4 *daily orally*
Calcium (mg/day)	Intake ..	540	540	540	540
	Fæcal ..	440	440	320	320
	Urinary..	116	148	200	236
	Balance..	−16	−48	+20	−16
Phosphorus (mg/day)	Intake ..	810	810	810	810
	Fæcal ..	380	380	290	300
	Urinary..	430	620	820	630
	Balance..	0	−190	−300	−120
Nitrogen (g/day)	Intake ..	12·8	12·8	12·8	12·8
	Fæcal ..	1·9	1·9	1·4	1·6
	Urinary..	11·3	10·0	11·0	10·4
	Balance..	−0·4	+0·9	+0·4	+0·8

Each column represents the mean daily values for successive three-day periods. (Period 1 commencing on seventh day of balance study.)

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phosphorus varied on four separate estimations from 2·1 to 2·9 mg. per cent and the serum calcium from 10·3 to 10·6 mg. per cent (5·15–5·3 m.eq./litre) and the alkaline phosphatase on two estimations was 6·5 K.A. units. The serum proteins were 8·0 grammes per cent and the A.G. ratio 1·6, with a normal pattern on electrophoresis. The serum electrolytes were normal. The creatinine and urea clearances were normal. The urinary pH after the ingestion of 8 grammes ammonium chloride fell to 4·9. The phosphate clearance (when the serum inorganic phosphate was 2·1 mg. per cent) was 7·7 ml./min. and the ratio between phosphate and creatinine clearances was 0·075 (Table III, p. 145). This indicated a marginal phosphate-losing renal lesion. Renal function, apart from this one defect, was very good.

X-ray examination of the pelvis in December 1957 revealed a considerable increase in the protrusio acetabuli on the left side where the head of the femur now appears to have penetrated the acetabular cavity.

He was last seen in the Out-Patient Department in September 1959 when his main complaint was that of impotence. He was working as a porter in a hospital and he felt that he was having much less pain than usual. He has been on oral Calciferol for three years, the dose ranging between 50,000 and 125,000 units, depending on the serum-calcium levels.

On 18.8.59 the serum calcium was 12·3 mg. per cent, serum inorganic phosphate 4·7 mg. per cent and the alkaline phosphatase 3·7 K.A. units.

He would not agree to discontinuing his Calciferol for three months so that renal function studies could be repeated as he considered the medicine had been very helpful to him.

Case 2.—D. G. (II 8), female, aged 32 years. N.H. No. 66299. This patient, a domestic servant, was admitted to the National Hospital on June 15, 1956, under the care of Dr. J. Purdon Martin. Four days before her admission she had been found paralysed in all four limbs after falling down a flight of stairs.

In her youth she had been an average scholar and able to run and take part in sport as well as her fellow scholars. She had never had any bony injuries. For as long as she could remember she had had a crooked back. She denied any difficulty in walking or climbing stairs during the period she was at work, but her employers reported that they noticed her rather unsteady and clumsy on her feet. They had the impression too that her right arm was a little weak.

On June 11, 1956, while carrying a bundle of linen, she fell down a flight of stairs. She could not recall whether this was the result of any accident or not or whether some other circumstance such as sudden weakness in the legs had been responsible. She lay unconscious for a few minutes and there could well have been, in addition, momentary retrograde amnesia. On recovering consciousness she was unable to move her arms or legs. She was admitted to another hospital where she was found to be totally tetraplegic. She developed retention of urine. The following day a lumbar puncture was performed. The cerebrospinal fluid was at a pressure of 155 mm. and there was a very poor and delayed rise and fall in pressure on jugular compression. The fluid contained 500 red cells/c.mm., 5 lymphocytes/c.mm. and a protein of 60 mg. per cent. A little return in power in the arms was noted over the next two days. On admission to the National Hospital on June 15, 1956, her condition was as follows: she was of average intelligence; her height was 56 in., span 62 in. and crown to pubis measurement 27½ in., indicating loss of height; she had striking prognathism and a short neck: there was bulging of the temporal regions of the skull. She had a marked kyphoscoliosis. Her visual acuity was 6/12 in the right eye and perception of hand movements in the left eye. The right optic disc was normal. The left eye showed scattered opacities in the media and there was a high degree of myopia with severe myopic retinal changes. The visual fields were full. She had a left Horner's syndrome. Both pupils reacted to light. She had

coarse horizontal nystagmus at rest and on looking in all directions. The corneal reflexes were diminished but there was no impairment of cutaneous sensation on the face, and the function of the motor portion of the trigeminal nerve was normal on each side. There was slight right facial weakness. The palate moved weakly in the mid-line. The tongue protruded to the right and there was gross wasting of the right half of the tongue with fasciculations. Tone was decreased in the upper limbs and grossly increased in the lower limbs. She could not move any muscle in the limbs voluntarily against gravity. Movement, with gravity eliminated, was possible in the pectoralis major on both sides, and flexion of the wrist and fingers was possible on the left. A flicker of movement was seen in several muscle groups in the limbs. There was no wasting and no scars on the skin suggesting previous burns.

Sensation to pin-prick was abnormal below C2 level, there being hypalgesia except in the area below the costal margin on the left side where pin-prick had an unpleasant quality. Cotton-wool sensation was impaired below C2. Vibration sense was absent below the clavicles and joint position sense grossly impaired in the arms and legs. The jaw-jerk was brisk. The biceps-jerks were diminished and there was associated finger flexion. The right supinator jerk was very weak and the left was present with marked finger flexion. The triceps-jerks were normal. The finger-jerks were brisk. The knee-jerks were very increased. Both legs were held in plantar flexion at the ankle, and there was bilateral knee and ankle clonus. Both plantar responses were extensor. There was retention of urine. The teeth were widely splayed and misshapen.

Investigations on admission.—X-ray examination of the skull showed a very marked degree of basilar impression, Bull's angle being 58 degrees (fig. 4). There was considerable widening of the cervical spinal canal. X-ray examination of the dorsal spine showed some collapse of the bodies of D 9 and 10 vertebræ. X-ray examination of the pelvis showed slight deficiency of calcification, flattening and protrusion of the right acetabulum (fig. 5). The long bones were abnormally thin. Other special tests gave the following results: Blood HB 77 per cent. W.B.C. 6,500 per c.mm. E.S.R. 20 mm. in one hour (Wintrobe). Blood group B Rh+. Serum calcium 10 mg. per cent. Serum phosphate 4·1 mg. per cent. Alkaline reserve 25·7 m.eq./litre. There was a trace of protein in the urine and no glycosuria and no abnormal casts. The clinical diagnosis was one of basilar impression with syringomyelia. The nature of the lesion producing the sudden tetraparesis was uncertain but it was thought it could have been a hæmorrhage into the syringomyelic cavity. Exploration of the cervical cord was decided and on June 16, 1957, Mr. Harvey Jackson performed an upper cervical laminectomy. At operation spina bifida of the upper cervical vertebræ was seen. The dura mater of the cervical cord was then opened in the mid-line. The cervical cord thus exposed was noted to be unusually wide, and it was also noted that the left cerebellar tonsil had herniated considerably through the foramen magnum. A needle was inserted in the mid-line in the upper part of the spinal cord and 20 c.c. of clear colourless fluid were aspirated. The centre of the cord was then incised (after preliminary diathermy) for a distance of 5 cm. As a result of this procedure a large intramedullary cavity was exposed (fig. 6). When measurements were made with a catheter, the length of this cavity was found to be 16 cm., of which 3 cm. extended into the medulla. The shell of nervous tissue surrounding the cavity was so thin that anteriorly the anterior longitudinal fissure could be clearly seen as a cleft bridge of theca. The wall of the cavity was smooth but not uniformly regular. A small biopsy of the cavity of the cord was taken. The dura was not closed.

Biopsy report on portion of cervical cord (Dr. W. Blackwood).—The layer of astrocyte gliosis is not dense enough to make the diagnosis certainly one of

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syringomyelia, nor is there a lining of ependymal cells which would make the diagnosis of hydromyelia more likely. The fluid from the cyst was clear with no red cells, 1 lymphocyte and 3 large mononuclear cells per c.mm. and its protein content was less than 10 mg. per cent.

Progress.—The patient was not further upset by the operation. After a day there was a very slow return in power in the lower limbs. After two weeks she could lift the left leg 3 in. off the bed and, with gravity eliminated, could flex and extend the right hip and both knees. A little movement appeared in the ankles but the feet were held strongly plantar-flexed. There was no change in the signs in the cranial nerves nor in the sensory signs on the trunk and limbs. The tendon reflexes in the arms were now extremely brisk and tone was increased in all four limbs. The abdominal reflexes were absent. The knee and ankle jerks were increased with clonus and the plantar responses remained strongly extensor. She had an indwelling catheter in position. She remained in the hospital for more than two years but there was little further improvement in power. Flexor spasms in the legs were troublesome for a period. Constipation and urinary infection were prominent features for several months. By January 1958, however, the catheter could be withdrawn as she had developed an automatic bladder emptying every two to three hours. Examination recently showed that there was now moderate power of flexion of the thumb and of the index, middle and ring fingers of the right hand. The hyperpathic response to pin-prick was still present in the left leg.

Further investigations.—Accurate metabolic balance studies were at first hindered by the obstinate constipation and the concomitant urinary infection. A fat balance over a period of six days was normal (97·8 per cent absorption). The amino-acid nitrogen in the urine was 462 mg. in twenty-four hours (urinary volume 1,600 ml.) and on chromatography a normal pattern of amino-acids was found. A urea concentration test was normal. The blood urea was 38 mg. per cent and urea clearance 45 per cent. In May 1957 the patient was started on calciferol, 100,000 units daily, by mouth, but because of the severe muscle weakness it was difficult to judge improvement. This treatment was discontinued after four months.

The patient was also investigated under the care of Professor F. T. G. Prunty at St. Thomas's Hospital. It was found on four occasions that her serum calcium (9·6 to 10·6 mg. per cent), plasma inorganic phosphorus (3·3 to 3·5 mg. per cent) and alkaline phosphatase (7 to 9 King-Armstrong units) were normal, as were the theoretical renal phosphorus threshold (2·5 mg. per cent) (Hyde *et al.*, 1959) and the plasma electrolyte concentrations (in mEq/L: sodium 136, potassium 4·4, chloride 100, bicarbonate 30). Biopsy of bone from the iliac crest showed "Cortical trabeculæ thinner than normal, and reduced in number; a mosaic pattern of the trabeculæ, but no evidence of increased bone formation or of osteoclasis. These are the appearances of osteoporosis" (Dr. J. L. Pinniger).

Calcium balance was also measured during a twenty-eight-day period (8.9.58 to 4.10.58, *see* Table II). The high fæcal calcium (935 mg./day) suggested the possibility of vitamin D deficiency or resistance. On questioning it was noted that the patient had a small and capricious appetite which reduced her vitamin D intake to approximately 60 units per day. She was therefore returned to the National Hospital and given 5,000 units of calciferol daily. After one month of this therapy, she was given the same diet as that which she had during the above balance studies: fæces collected over four weeks (13.12.58 to 9.1.59) contained 538 mg./day of calcium (Table II). Therapy with 5,000 units of calciferol daily continued and, after a total of four months, she returned to St. Thomas's Hospital for repetition of balance investigations; fæcal calcium was now (26.3.59 to 23.4.59, Table II) 712 mg./day, and the balance was slightly negative. Serum calcium was 9·6, 10·0 mg. per cent, plasma phosphorus 3·5, 3·4 mg. per cent, alkaline phosphatase 8, 7 King-Armstrong units.

TABLE II.—CALCIUM, PHOSPHORUS AND NITROGEN BALANCE ESTIMATION ON D.G. (II 8)

		8.9.58 to 4.10.58	13.12.58 to 9.1.59 *Calciferol*	26.3.59 to 23.4.59 5,000 *units daily orally*
Calcium (mg./day)	Intake ..	723		748
	Fæcal ..	935	538	712
	Urinary..	68		63
	Balance..	−280		−27
Phosphorus (mg./day)	Intake ..	767		810
	Fæcal ..	332		399
	Urinary..	398		345
	Balance..	+37		+66
Nitrogen (g./day)	Intake ..	6·4		6·5
	Fæcal ..	0·3		0·4
	Urinary..	7·0		5·8
	Balance..	−0·9		+0·3

Case 3.—B. G. (II 6), female, aged 38 years. She had no symptoms and works at present as a domestic servant. She was a good scholar at school and had noticed no difficulty in walking or running. She claims to have always enjoyed good health.

On examination.—She was a person of average intelligence. She was small in stature and had a strong resemblance to her sister (fig. 7) with a degree of prognathism. Her height was 59 in., span of arms 57 in., and crown to pubis measurement was 28 in. She had a slightly short neck and slight upper dorsal kyphosis. The chest mildly overhung the abdomen. The cranial nerves were normal. Examination of power, tone and sensation revealed no abnormality in the limbs. The tendon reflexes were all brisk, the abdominal reflexes present but both plantar responses were definitely extensor in type. General medical examination was normal. She had five upper and seven lower teeth remaining. It was noted that the incisor and canine teeth had somewhat transparent edges.

Investigations.—Dr. M. D. Milne kindly arranged the admission of this patient to the metabolic ward in Hammersmith Hospital. Serum calcium, phosphorus and alkaline phosphatase were within normal limits. There was no evidence of abnormal excretion of phosphate in the urine (Table III). A calcium and nitrogen balance

TABLE III.—SUMMARY OF METABOLIC DATA ON B. G., R. G., AND D. G. (II 6, II 7 AND III 4)

	Serum Ca (*m.eq./l*)	*Serum P* (*mg. per cent*)	*Alk. phosphatase* (*K.A. units*)	*Phosphate clearance* / *Creatinine clearance*	*Minimum urinary pH after ingestion of 8 grammes* NH_4Cl
II 6 B. G.	5·4	3·3	5·0	0·14	5·2
II 7 R. G.	5·2	2·1	6·5	0·075	4·9
III 4 D. G.	5·3	3·2	29	0·11	4·9

study over six days was normal. Unfortunately the patient would not agree to remain in the hospital for a longer period.

Serum electrolytes and serum protein were normal. Hæmoglobin 75 per cent and the blood film indicated an iron-deficiency anæmia. Blood group B Rh +.

X-ray of the skull showed a degree of basilar impression with Bull's angle 22 degrees (fig. 8). The upper limit of normal is 13 degrees (Bull *et al.*, 1955). Wormian bones were present in the skull. X-ray of the pelvis showed slight flattening and thin pubic rami. X-ray of the hands and cervical spine were normal. Bone biopsy from iliac crest (Prof. Harrison). "No evidence of osteomalacia. There is a rather complex pattern of Haversian canals."

Case 4.—D. G., male, aged 8 years (III 4). Son of Case 1. The child appeared healthy and normally proportioned. The first dentition started at a normal eruption time but were small and badly shapen and shedding commenced at three years. The second dentition started age 7 years and were imperfectly formed and erupted in an irregular fashion. The child reached the milestones of sitting up, talking and gaining bladder control at a normal age but walking was delayed. He was said to have had a dislocated hip and was treated at another hospital for fourteen months. He was able to walk at age 3½ years and he now has unrestricted activities for a boy of his age.

On examination his teeth were badly shaped and had a peculiar translucent and brownish colour. A dental opinion indicated that this corresponded to the condition of dentinogenesis imperfecta.

No abnormal signs were found on neurological examination. He had 3 pigmented moles on the front of the thorax.

Investigations.—X-ray examination of the skull was first carried out in 1953 and Dr. Bull reported that there may be some basilar impression but that the margin of the hard palate is ill-defined. Four years later there was no change in the X-ray appearances of the skull. A few Wormian bones were noted in the X-ray of the skull.

Serum calcium and phosphorus were normal but the alkaline phosphatase was 29 K.A. units.

This boy was studied by Dr. Milne in the metabolic ward of Hammersmith Hospital. Urinary excretion of phosphate was normal and acidification of the urine was normal (Table III). The urine contained 300 mg. of glucose in a twenty-four-hour specimen. Serum proteins and a blood count were normal. His Blood Group was B Rh +.

Case 5.—I. G. (III 5), female, aged 22 months. Daughter of Case 1. This baby was only briefly examined but there was no clinical evidence of bone disease and no abnormal neurological signs. X-ray of the skull showed a slightly flattened basal angle but no evidence of basilar impression. A few Wormian bones were present.

Discussion

In the family described 3 out of 5 siblings showed basilar impression.

In Cases 1 and 2 there was unmistakable evidence for the presence of a generalized bone disease.

Nature of bone defect.—The bone disease clearly appears to be inherited. Metabolically it is characterized by normal values for serum calcium, phosphorus and alkaline phosphatase except for a single low serum phosphorus (2·1 mg. per cent) in Case 1. The tests of renal tubular function are also normal except for the ratio of phosphate to creatinine clearance in Case 1 measured

at the same time as the above low serum phosphorus concentration; it may be noted that a small downward error in the estimation of the serum phosphorus would not only raise the ratio, in the direction of abnormality, but also alter the interpretation, which depends partly on the serum phosphorus concentration, in the same direction (McGeown, 1957). The prompt increase in urinary calcium excretion which followed the administration of calciferol (*see* Table I) is further evidence against osteomalacia.

Fat balance studies excluded steatorrhœa.

The calcium balance study in Case 2 which disclosed an abnormally high fæcal calcium, raised the question of vitamin D lack or resistance. Her dietary history supported the possibility of deficiency and the normal response to a low calciferol dose appears to exclude the likelihood of resistance.

The bone histology in Cases 2 and 3 was not that of osteomalacia.

The balance of evidence is in favour of an inherited osteoporosis, probably osteogenesis imperfecta. The manner of presentation is unusual. Only in Case 1 was there a history of previous skeletal fractures. None of the members of the family demonstrated blue sclerotics. Thoma (1950) states that dentinogenesis imperfecta which has a dominant inheritance occurs in diseases affecting bone formation (especially osteogenesis imperfecta). Case 4 is an example of this dental abnormality. His father (Case 1) had bad teeth from infancy. Both his aunts (Cases 2 and 3) appeared to have a similar though milder dental condition.

Skeletal deformities including basilar impression are found in osteogenesis imperfecta (Caniggia *et al.*, 1958) but neurological symptoms and signs resulting from skull deformities have only been infrequently reported (Ray, 1942; O'Connell and Turner, 1950).

In Case 3 basilar impression was definitely present. The evidence for osteogenesis imperfecta was provided by the prognathism, the poorly shaped dentition and the positive family history.

Certain points which may have considerable significance in the pathogenesis of basilar impression in this patient require emphasis. The first weight bearing, undertaken by the infant, is the support of the head in the first six months. The size of the infant's head is disproportionately large compared to the cervical spine, and it grows more rapidly than other structures in the first year of life. In addition, as Mellanby (1944) pointed out in his experiments on puppies, the contents of the posterior fossa increase in weight to a degree of 17 per cent more than the rest of the intracranial structures. It is conceivable then that a degree of bone softening may be present allowing basilar invagination but not sufficient to produce clinically recognizable deformities elsewhere.

The relationship between basilar impression, syringomyelia and

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cerebellar ectopia.—In Case 2 an advanced degree of intra-medullary cavitation of the cervical cord was found. The problem is whether this represented another congenital malformation, i.e. syringomyelia, or was secondary to chronic obstruction in the region of the foramen magnum, i.e. hydromyelia. The presence of spina bifida in the first four cervical vertebræ in this patient favours the former view. Spillane *et al.* (1957) discuss the association of basilar impression and syringomyelia in patients with congenital malformations near the foramen magnum. They support the view that the vast majority are due to a distinct and separate malformation. In their series, however, all 14 cases with syringomyelia did in fact have basilar impression as well. These authors, however, accept that intramedullary cavitation of the cord can occur as a direct result of severe basilar impression.

O'Connell and Turner (1950) and Spillane (1957) discuss the mechanism of intramedullary cavitation and in particular the role of impaired blood supply in patients with basilar impression. Russell and Donald (1935) and Russell (1949) support the occurrence of hydromyelia in the Arnold-Chiari malformation, and they relate the malformation to the presence of basilar impression. Cases 1 and 2 showed the presence of cerebellar ectopia. In the case reported by Ray (1942) with osteogenesis imperfecta and basilar impression, the tonsils of the cerebellum were found at operation displaced down to the level of C.2. Mellanby (1944) gives impressive support for the production of cerebellar ectopia by the overgrowth of the basal bones reducing the volume in the posterior fossa in vitamin-A-deficient puppies. He does not describe intramedullary cavitation but the experimental period was short. There is thus reason to believe that the intra-medullary cavitation of the cord in Case 2 and the cerebellar ectopia in Cases 1 and 2 could have been the direct result of basilar impression, which was secondary to osteogenesis imperfecta.

Wormian bones.—Cases 1, 3, 4 and 5 were found to have Wormian bones radiologically. Torgersen (1954) makes the interesting suggestion that these supernumerary skull bones are favourable in allowing an increase in the length and breadth of the skull. Torgersen (1951) notes the familial incidence of Wormian bones. Another example (perhaps the first) of familial incidence of Wormian bones is described by Keiller and Piggott (1938) in 4 of 7 skulls believed to belong to a family found in an archæological dig at Lanhill Barrow. Wormian bones are very common in osteogenesis imperfecta (Pendergrass *et al.*, 1956).

Management.—Both children will be carefully followed up with regard to the development of basilar impression and the bone disease. The case reported by Ray (1942) is of interest in that progression in the severity of the basilar impression over a period of eight years was noted radiologically.

SUMMARY

A family is described in which 3 of 5 siblings had basilar impression and osteogenesis imperfecta. The occurrence of intramedullary cavitation of the spinal cord in basilar impression is discussed. A familial incidence of Wormian bones and dentinogenesis imperfecta is reported.

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THE RELATIVE VALUES OF THE MARCHI METHOD AND SOME SILVER IMPREGNATION TECHNIQUES

A Critical Survey

BY

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" 'Tis a pleasant Spectacle
to behold the Shifts,
Windings, and Caprichios of
distress'd Nature, when
pursued by a close and well-
managed Experiment."
JOSEPH GLANVIL, F.R.S., 1664.

In recent years silver impregnation methods have come into more and more general use for the experimental tracing of fibre connexions in the central nervous system. A number of papers have been published dealing with the technical aspects of the various methods of this type, and their advantages and drawbacks have also been discussed to some extent. However, although those using one or more of the silver impregnation methods in their studies are well aware of the relative merits of these methods and the classical Marchi method, among some workers in the field of neurological sciences this is apparently not so, as can be gathered from oral and written statements. A natural veneration for the time-honoured Marchi method has led many to cherish a scepticism towards these "new" methods which is not justified. The purpose of this survey is to present an evaluation of the pros and cons of the Marchi method versus silver impregnation methods, and to discuss some points of relevance to the usefulness of the various silver techniques.

The discovery by Marchi in 1886 of a staining method which would selectively impregnate degenerating myelin gave a great impetus to neuroanatomical research. Indeed, between this date and the outbreak of the First World War, that is, within a space of three decades, an immense amount of work was done, both on man and lower animals, with the help of this technique. It was during this period that the main

outlines of classical neuroanatomy, as set out in current textbooks, were laid down by the use of the Marchi method. Tracts were mapped out and named, origins and terminations established, and functional implications discussed. One need only recall such names as (at random) Collier and Buzzard, Kohnstamm, Lewandowsky, Petrén, Probst, Rothmann, Wallenberg, to realize how very great is the debt which all modern neuroanatomists owe to these early workers. Their individual output was colossal; and the accuracy of many of their descriptions is a fact to which any present-day research worker in this field can testify with awe.

The Marchi method continued and continues to be used after 1914, but less extensively than in the period before this date. Between the wars, however, the work of Le Gros Clark (1936) and Walker (1938) on the afferent connexions of the thalamus may well serve to illustrate the very valuable new facts which could still be elucidated by means of this technique. Moreover, in many laboratories new modifications of the method showing better impregnation of degenerating myelin and less artefact, were developed. The best known and most used of these is that of Swank and Davenport (1934), and valuable contributions to our knowledge of neuroanatomy are still being made with the Marchi method.

But even during what might be called the hey-day of the Marchi method, Bielschowsky (1904) introduced his technique of silver impregnation. As all subsequent silver methods are essentially modifications of this, it may be worth while at this juncture to stress that silver impregnates the neuron itself, and not its surrounding myelin sheath. Thus the amount of detail which can be seen by these methods depends on the fineness of grain of the impregnation. To this end of securing more precise detail, numerous modifications of the original Bielschowsky method have been introduced; notable among these are those of Bodian (1936) and Holmes (1943). It had been recognized quite early that if sufficiently fine-grain impregnation of the axon and its terminal processes could be obtained, it should be possible to recognize degenerative changes in them. Early reports on such material include those of Hoff (1932); Hoff and Hoff (1934); Gibson (1937), and Szentágothai (1941, 1942).

In 1946, Glees published the modified Bielschowsky technique which now bears his name. This method, when successfully applied, impregnates all axons and their processes with a very high degree of delicacy, and a varying number of normal boutons are commonly seen. The most usual appearance of normal boutons in silver impregnated material is that of a hollow ring, but several other forms have been described (for example by Phalen and Davenport, 1937; Minckler, 1940). The variations of normal boutons as seen in sections prepared according to

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the Glees method have been discussed by Blackstad, Brodal and Walberg (1951) and Rossi and Brodal (1956). Figs. 3 and 4 (Plate XXVI) serve to illustrate this point.

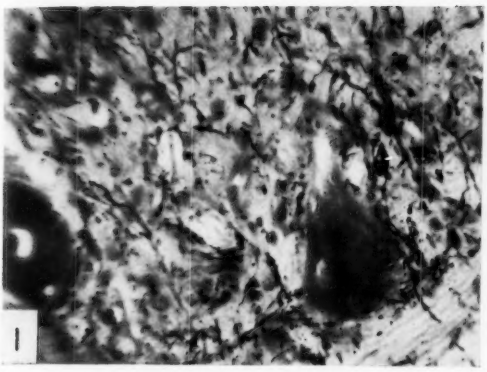
A somewhat different approach has been taken by Nauta. His original procedure (Nauta, 1950), yielding results largely corresponding to those obtained with the Glees method, has later been modified (Nauta and Gygax, 1951, 1954), and recently the use of the Laidlaw solution as suggested by Chambers, Liu and Liu (1956) has been adopted (Nauta, 1957). In this method impregnation of most normal axons is usually suppressed, so that only degenerating fibres are seen, as in the Marchi method—but with the significant difference that axoplasm is impregnated. This differential impregnation of degenerating axoplasm has been achieved at some sacrifice to the fineness of detail as compared with the Glees method, and there is general agreement that the Glees method is capable of impregnating terminal filaments of finer calibre than is that of Nauta (*see*, for example, Glees and Nauta, 1955; Evans and Hamlyn, 1956; Adey *et al.*, 1958). But the Nauta method has the advantage of Marchi-treated material that areas containing degenerating fibres can easily be seen even with low powers of the microscope, thus saving a great deal of time as well as the necessity for systematic examination of whole sections with the oil immersion lens.

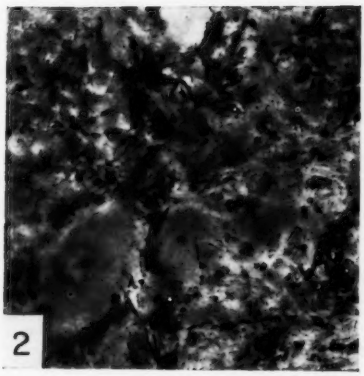
We have recently carried out an investigation on primary vestibular afferent fibres in the cat (Walberg, Bowsher and Brodal, 1958) in which alternate sections were treated by the methods of Glees and Nauta. The same approach is currently being used at the Anatomical Institute in Oslo in an experimental study of the fastigiovestibular connexions in the cat. Observations made on these materials form a suitable basis for comparison of the two impregnations, and for discussion of their relative merits. Furthermore it would seem opportune to use these materials to compare the results obtained severally by Marchi and silver techniques.

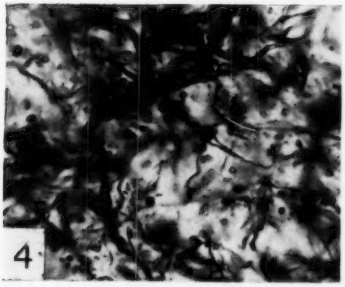
As is well known a successful Nauta (1957) section gives a clear picture of the course of degenerating nerve fibres which appear black on a yellow background. Frequently an identification of topographical landmarks is possible. There is unanimity among workers employing this method that it is well suited for tracing degenerating fibres of a tract, particularly when a small number of such fibres are intermingled with a majority of normal ones. A particularly illuminating observation bearing on this problem was made in the study of the fastigial efferents referred to above. Following lesions of the fastigial nucleus moderate numbers of degenerating fibres are constantly seen in the medial longitudinal bundle, mostly on the contralateral side (fig. 7).

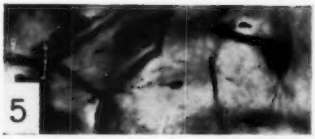
Compared with the Marchi method, the Nauta method has the advantage that artefacts are more easily distinguished from true

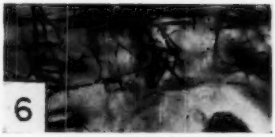
PLATE XXVI

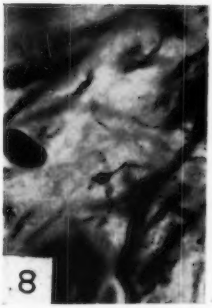


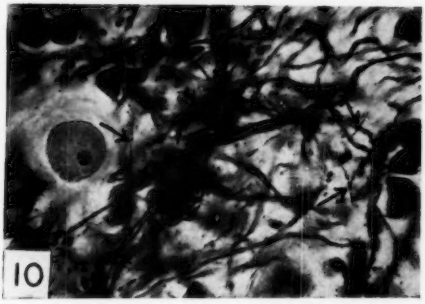












To illustrate article by David Bowsher, Alf Brodal and Fred Walberg.

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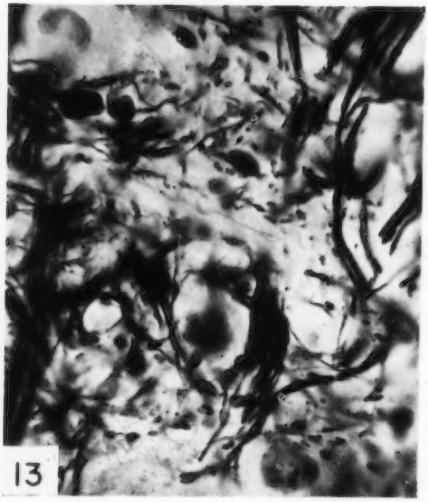

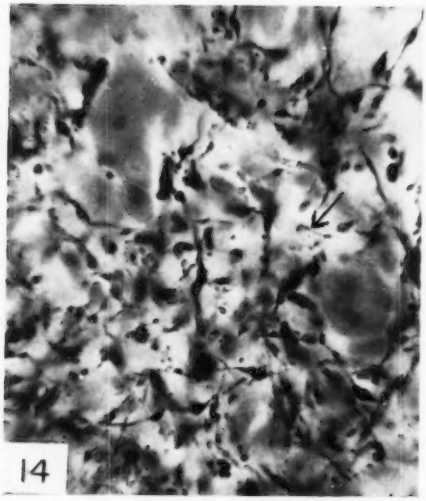

To illustrate article by David Bowsher, Alf Brodal and Fred Walberg.

degeneration, as mentioned by Evans and Hamlyn (1956). Furthermore, finer arborizations of the degenerating fibres can be seen, thus permitting more definite conclusions as to the actual site of termination. As examples of the use of the Nauta method in this way may be mentioned the study of reticulothalamic fibres by Nauta and Kuypers (1958) and of spinoreticular fibres in man by Bowsher (1957).

While the Glees method, like the Nauta method, can be used to follow degenerating fibres within a tract, it is more laborious and difficult, because one would have to search very carefully under oil immersion for degenerating fibres among the many normal ones which are also impregnated. It is of some importance to realize that with both methods it is almost essential that the fibres are cut longitudinally, particularly when the number of degenerating fibres is small. Thus, in the case of the fastigial fibres to the medial longitudinal fasciculus, referred to above, these were seen only in longitudinal sections, while they could not be identified in transverse sections.

With regard to determining the site of termination of degenerating fibres most authors agree that the Nauta and Glees methods are not of equal value. The Nauta (1957) method gives an excellent outline of an area of fibre degeneration (figs. 11 and 12), which can be seen with the low powers of the microscope. At the same time, one can compare the intensity of degeneration in different parts of the same field or section. With higher magnifications, it is possible to determine the relative calibre of the degenerating preterminal fibres. However, like other authors comparing the two methods (Glees and Nauta, 1955; Evans and Hamlyn, 1956; Adey *et al.*, 1958; Szentágothai and Rajkovits, 1958), we have found in our material that when it comes to the examination of the finest ramifications and the end formations of degenerating fibres, the Glees method is superior to the Nauta method.[1] In fact, only in Glees preparations are degenerating boutons (figs. 5, 6 and 8) (as well as a varying number of normal ones) and the finest degenerating fibres (figs. 9, 10 and 13) impregnated. In Nauta sections one commonly sees nerve cells encircled by clearly degenerating fibres, frequently referred to as "pericellular arborizations" (figs. 1, 2 and 14), but it is usually not

[1]In order not to create confusion, the term "terminal degeneration" should be applied only to degenerating terminal boutons and the very fine fibres leading up to them. On account of the wide variations which exist between the appearance of terminal boutons in normal material, a bouton should not be considered as degenerating unless it is enlarged, solid black, has more or less irregular contours and is connected with a "tail" of a disintegrating fine fibre (*see* Brodal and Gogstad, 1957; Pompeiano and Brodal, 1957). The finest degenerating fibres visible in Nauta preparations are generally of a somewhat larger calibre than the finest fibres in Glees material. The former, presumably, represent preterminal fibres, and the term "preterminal degeneration" should be used when referring to degeneration of these fibres.

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possible to decide whether this represents a type of synaptical contact. In any case, in our Nauta preparations we have never seen pictures resembling those shown in figs. 5, 6 and 8. Corresponding observations have been made by Evans and Hamlyn (1956) who assume that "the Nauta technique stains altered lipid substances in the degenerating nerve fibres."

In our material the Glees and Nauta sections have given concordant results in so far as the regions showing the finest degenerating fibres in Nauta preparations, i.e. preterminal degeneration (*see* footnote, p. 153) are identical to those in which terminal degeneration is found in Glees preparations. However, if information of the type of synaptical contact present is desired, Glees sections are essential. The value of this method in this respect is evidenced by findings such as the following: In several instances it has been possible to decide that afferent fibres to a nucleus end with terminal boutons on cells of different types. This is the case, for example, with the spinal afferents to the lateral reticular nucleus (Brodal, 1949) and to the nucleus reticularis gigantocellularis (Rossi and Brodal, 1957). On the other hand, practically all giant multipolar cells of the nucleus of Deiters as seen in Glees sections appear to be devoid of primary vestibular afferents (Walberg, Bowsher and Brodal, 1958), while the cerebellar (unpublished) as well as the spinal afferents (Pompeiano and Brodal, 1957) end on cells of all types. It may also be decided whether synaptical contact is made with perikarya of the cells only or with cell processes as well.

From our experience we would, therefore, conclude that if it is wished to study the course of fibres belonging to a tract, or scattered fibres spread over a larger area, the Nauta method is superior. If one is not concerned with establishing finer details in the termination of afferent fibres within a nucleus, one may as well use the Nauta as the Glees method. However, the additional information yielded by the latter obviously is of great interest for physiological problems.[1]

Nauta sections can be studied without using the immersion lens, while a study of Glees preparations necessitates laborious scrutiny of the sections under oil immersion in order to identify the degenerating structures occurring among a large number of normal fibres which are also impregnated. This fact probably explains why the Nauta method apparently has become more popular than the Glees method. Another point also deserves mention. As a bouton-like structure cannot safely be

[1]Exceptions may, however, exist to the conditions discussed above. In the study of the fastigiovestibular fibres it was found that occasionally very fine degenerating fibres are seen in the small cell group x of Brodal and Pompeiano (1957) in Nauta sections (fig. 14). These fibres are almost of the same small calibre as the finest ones which can be seen in the same group in Glees preparations (fig. 13), even if terminal boutons cannot be found.

interpreted as degenerating unless it is attached to a degenerating terminal filament (as mentioned, footnote, p. 153), it is necessary that it be in the plane of the sections. This means that a large number of degenerating boutons as well as fibres are not seen as such in these sections, which should not be more than 15 μ if satisfactory results are to be obtained. When it comes to photography through an oil immersion objective, even fewer degenerating structures can be demonstrated in the focal plane. While numerous degenerating boutons may, therefore, be present in the field photographed, only a few can be caught on the photographic plate (*see* figs. 5, 6 and 8). The reader not aware of this is liable to misjudge the documentary value of photographs of Glees preparations. With the Nauta method on the other hand, thicker sections can be used (45 μ), and as photographs can be taken at a lower magnification, a better impression of the quantitative distribution of preterminal degeneration is gained (figs. 11 and 12).

Needless to say, the silver impregnation methods, like all other methods, are hampered by the occurrence of artefacts. It is not our purpose here, however, to discuss the criteria of degeneration and the recognition of artefacts, as these items have already been the subject of attention by several authors (Glees and Nauta, 1955; Rossi and Brodal, 1956; Walberg, 1956; Nauta, 1957; Bowsher, 1957). Those having some experience with these methods will usually have little difficulty in distinguishing artefacts from true degeneration. As always, the reliability of findings described depends as much on the observer as on the method employed.

A few words should be devoted to the fact that some authors have reported negative findings with one or the other silver impregnation method where other observers have found positive evidence of termination of fibres. Such discrepancies may be due to different species having been employed, as is well known to those having experience with the methods.[1] This question has been commented upon by Glees and Nauta (1955), Evans and Hamlyn (1956) and Nauta (1957). Furthermore, the time factor may differ with the animal species, and, as mentioned, for example, by Nauta (1957), it may even not be the same for various fibre systems in the same animal. Possibly, biochemical factors may be involved. A too long fixation may be detrimental to the results of the Nauta method (Nauta, 1950, 1957) while this factor is apparently not of the same importance for the Glees method. It follows from the above that a negative finding in silver impregnation studies should not be taken as decisive evidence that a positive finding obtained with another silver impregnation method or in another animal species, is not correct,

[1]Cowan and Powell (1956) described a selectively distributed "pseudodegeneration" in Glees preparations from the hypothalamic region of the normal monkey, while Adey *et al.* (1958) were unable to verify this in Glees, Nauta and Bodian sections in the same animal. No explanation of this curious discrepancy can be adduced.

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or cannot be applied generally. This is true particularly when negative findings in Nauta sections are contradicted by positive findings made by the Glees method. For example, the Nauta method gave inconclusive results concerning the corticofugal fibres to the inferior olive (Kuypers, 1958), while Walberg (1956) could determine their terminal distribution precisely with the Glees method. In Glees sections unequivocal evidence has been presented that in the cat corticofugal fibres terminate in the principal as well as in all subdivisions of the spinal trigeminal nucleus and in the nucleus of the solitary tract (Brodal, Szabo and Torvik, 1956). When Kuypers (1958) did not find those passing to the principal trigeminal nucleus and the nucleus of the solitary tract in the same animal, this may be due to a failure of impregnation of the terminal parts of the degenerating fibres in his case, particularly since Szentágothai and Rajkovits (1958), also in Nauta material of the cat, confirmed the findings of Brodal, Szabo and Torvik (1956).

On the other hand, negative findings in Glees material when opposed by positive findings in Nauta sections may also be caused by species differences, or the time factor. But in addition it may happen that a moderate number of degenerating boutons or terminal fibres may be overlooked or be too small to be considered significant. This is easily explained by the circumstance emphasized above, that all the normal fibres and boutons are impregnated along with the degenerating ones in Glees sections. Expecially in nuclei where there is a large number of passing fibres, sparse degeneration in Glees sections is apt to be overlooked.

It remains to examine the merits of silver versus Marchi techniques. Perhaps because of our reverence for the pioneers mentioned at the beginning of this article, even today some neurologists are inclined to regard the Marchi method which these workers used as far more reliable than the silver methods. This is not in fact the case; indeed, as everybody having worked with both methods knows, it may be almost as capricious as silver. Many conflicting results have been obtained with the Marchi technique, by excellent workers, which have led to vivid scientific debates. We may cite as an example the controversy over spinotectal fibres. Von Sölder (1897) considered the spinotectal projection to pass only to the ipsilateral inferior colliculus, while Bruce (1898), Russell (1898) and Stewart (1901) considered it to pass to both inferior colliculi from one side of the cord. On the other hand, Thiele and Horsley (1901) considered this pathway to end entirely in the superior colliculi.

Artefact can be as much a bugbear to Marchi preparations as to those made with silver—perhaps even more so. Marion Smith (1956), one of the most experienced users of the Marchi technique, has written that "... the method ... is marred by the frequent occurrence of artefacts."

She further goes on to state: "Some artefacts resemble true degenerating fibres seen in transverse section, while others resemble degenerating fibres in longitudinal section." The "Marchi dust" which is supposed to indicate the termination of a fibre bundle is difficult if not impossible to distinguish from the generalized deposit which may occur as an artefact; whereas, in our opinion, it is usually possible (though not easy), with experience, to distinguish true degeneration from artefact in silver preparations. It is not only the terminal myelinated fibres which may be confused with Marchi artefact. As recently as 1951, Matzke has drawn attention to "pseudo-degeneration" of quite large fibres in the corpus striatum. It may be remarked parenthetically that a similar artefact ("myelin sheath" artefact of Nauta, 1957) is fairly constantly seen in this location with the Nauta silver impregnation.

When evaluating the Marchi versus the silver impregnation methods it is important to be aware that by its very nature, silver impregnation can reveal fibres and terminals which the Marchi method is incapable of showing. As a relevant example may be mentioned the question whether corticobulbar fibres end in the motor cranial nerve nuclei. Older workers using the Marchi method, arrived at conflicting conclusions (for references, *see* Walberg, 1957). It has recently been shown, however, that neither in Glees sections (Walberg, 1957) nor in Nauta sections (Kuypers, 1958; Szentágothai and Rajkovits, 1958) can such fibres be identified in the cat. The superiority of the silver methods for solving problems like this is due to the fact that silver can impregnate thin axons which do not possess a myelin sheath in the classical sense, and also impregnates (in the case of the Glees technique) boutons terminaux beyond the point at which the myelin sheath of the parent axon has disappeared. Thus the details of fibre or collateral termination cannot *ipso facto* be revealed by the Marchi technique; it is, therefore, impossible to use this to confirm findings concerning the termination of nerve fibres made with silver impregnation methods.

In the two silver methods with which we have been concerned different chemical constituents of the axoplasm must be impregnated. The Nauta technique will not work on alcohol-treated material, whereas the Glees impregnation is not affected by this (Evans and Hamlyn, 1956). Thus, if results given by both techniques in the same material are identical, as in our study of primary vestibular afferents and the study of fastigiovestibular fibres, we consider this corroboration to have greater validity in verifying the accuracy of the findings concerning the termination of nerve fibres than if the observations made by one or other of these methods are or are not "confirmed" by the use of the Marchi technique.

Summary

Following a brief survey of the historical development of anatomical

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methods used for tracing degenerating nerve fibres the relative advantages and drawbacks of the Glees and Nauta methods are discussed. Both methods are based on the affinity of nerve fibres to silver.

Studies, performed by the authors, in which the Nauta and Glees methods have been used on alternating sections show that there is good agreement between the results given by the two methods. However, they differ in some respects. With the Glees method all degenerating fibres, including finest terminal fibres and boutons ("terminal degeneration") are impregnated, making it possible to study details in synaptical connexions. Although there may be exceptions to this rule, in general the finest degenerating fibres which can be recognized with the Glees method are not impregnated with the Nauta technique, which thus brings out what may be called "preterminal" degeneration. Since the normal fibres are not stained in successful Nauta (1957) sections, degenerating fibres stand out clearly against the background. The method is, therefore, particularly suited for tracing the course of degenerating fibres, and it also gives clear pictures of their sites of termination. These can be recognized with low powers of the microscope, while the Glees method necessitates examination of the sections under oil immersion.

Even if, in general, the Glees and Nauta methods give concordant results, it may happen that a finding made with one method may be difficult to verify with the other. The reasons for this, which are largely technical, are discussed, and it is emphasized that a negative finding obtained by one of the methods only, should not be considered decisive.

The Marchi method, in which degenerating myelin is stained, cannot be used to verify findings made with one or other of the silver impregnation methods concerning the details in the termination of nerve fibres. There is no doubt that on these points silver impregnation methods are able to bring to light information which cannot be revealed in Marchi material. Artefacts may be as much a difficulty when evaluating Marchi preparations as when judging silver impregnation material. The belief that the Marchi method is more reliable for studying fibre connexions of the central nervous system than the silver impregnation methods is untenable.

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LEGENDS TO PLATES

PLATE XXVI

Untouched photomicrographs showing normal and degenerating fibres and boutons in Glees and Nauta sections.

FIG. 1.—Degenerating preterminal fibres, some of them forming "pericellular arborizations." From the lateral vestibular nucleus following a lesion of the fastigial nucleus in the cat. Nauta method. × 270.

FIG. 2.—Degenerating preterminal fibres as in fig. 1 in the pars magnocellularis of the spinal trigeminal nucleus in man, following a chordotomy. Nauta method. × 360.

FIG. 3.—Terminal boutons on a large cell process in the reticular formation of a normal cat. Note variations in size and shape of the boutons. Glees method. Oil immersion. × 850. From Rossi and Brodal (1956).

FIG. 4.—Normal terminal boutons in the inferior olive of the cat. Most boutons are small, but there are variations with regard to their impregnation. Glees method. Oil immersion. × 630.

FIG. 5.—A degenerating terminal bouton with a just visible "tail" of a degenerating terminal fibre in the inferior olive of the cat following a lesion of the mesencephalon. Glees method. Oil immersion. × 1080.

FIG. 6.—A terminal degenerating fibre ending with a degenerating terminal bouton in the reticular formation of the cat, following a lesion of the cerebral cortex. Glees method. Oil immersion. × 850.

FIG. 7.—Degenerating fibres in the medial longitudinal fasciculus of the cat, following a destruction of the contralateral fastigial nucleus. Nauta method. × 270.

FIG. 8.—A terminal degenerating fibre ending with a terminal degenerating bouton in the inferior olive of the cat, following a lesion of the mesencephalon. Glees method. Oil immersion. × 1080.

FIG. 9.—Terminal degenerating fibre in the raphe nucleus of the medulla in the cat, following a lesion of the cerebral cortex. Glees method. Oil immersion. × 850. From Rossi and Brodal (1956).

FIG. 10.—Terminal degenerating fibres (some of them marked with an arrow) in the inferior olive of the cat, following a lesion of the mesencephalon. Glees method. Oil immersion. × 630.

PLATE XXVII

FIGS. 11 and 12.—Low power views of Nauta sections showing areas crowded with preterminal degenerating fibres, following a lesion of one fastigial nucleus in the cat. FIG. 11: group x of Brodal and Pompeiano (1957). The borders of the descending vestibular nucleus (to the left) are indicated. FIG. 12: group f in the caudal part of the descending nucleus. × 74.

FIG. 13.—Degenerating terminal fibres in a Glees section from group x, following a lesion of one fastigial nucleus in the cat. Some coarser fibre fragments are also seen. Oil immersion. × 630.

FIG. 14.—From the same region and the same animal as in fig. 13, but from an adjacent section treated according to the Nauta method. Numerous preterminal degenerating fibres are present, but occasionally a very fine fibre (arrow) is seen which apparently has the same dimensions as the finest degenerating fibres seen in the Glees section of fig. 13. This is presumably a terminal degenerating fibre. Oil immersion. × 630.

CENTRAL CORTICAL PROJECTIONS TO MOTOR AND SOMATO-SENSORY CELL GROUPS

An Experimental Study in the Rhesus Monkey

BY

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Introduction

Previous degeneration studies in the cat demonstrated cortical projections to the medial parts of the pontine and medullary tegmentum, as well as to the spinal trigeminal complex, the adjacent lateral tegmentum and the region of the nuclei cuneatus and gracilis (Kuypers, 1958*a*). In primates, lesions of the "pre-central" face area likewise produced a degeneration in the lateral tegmentum. Additional degenerating fibres, however, which were lacking in the cat, distributed to the motor nuclei. On the other hand, such pre-central lesions produced hardly any degeneration in the spinal trigeminal complex (Kuypers, 1958*d*). Since in human material with lesions of the hemisphere (Kuypers, 1958*b*) degenerating elements were abundant in the spinal trigeminal complex as well as in the lateral tegmentum and the motor nuclei, the inference was made that the projection to this sensory nucleus originates primarily in the post-central "sensory" areas. This was confirmed in two monkey experiments (Kuypers, 1958*d*). These findings prompted a more general study regarding differential distributions from pre-central and post-central areas. The results of this study are reported.

Materials and Methods

In 19 Rhesus monkeys lesions were placed in the frontal, pericentral and parietal cortical areas. After fixation in 10 per cent neutral formalin, the pons and medulla oblongata were cut in frozen sections. Moreover, frozen sections were obtained from the upper cervical, low cervical, thoracic, lumbar and sacral parts of the spinal cord. These sections were impregnated following Chambers and Liu's (1956) modification of the Nauta-Gygax silver impregnation technique (1954).

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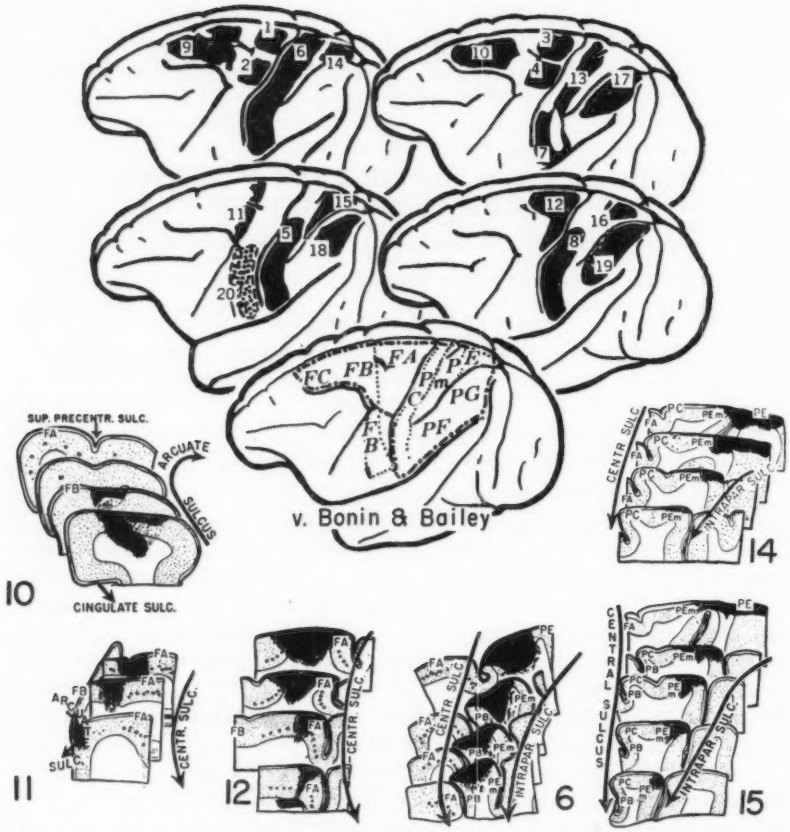

FIG. 1.—Diagram representing the location of the lesions, together with the cytoarchitectural subdivisions of the areas involved (von Bonin and Bailey, 1947). Tracings of serial sections through some of the lesions are reproduced.

The lesions were located as follows (fig. 1):

A. *Pre-central and Frontal Lesions*

Exps. 1 and 3. Lesions of the upper one-third of the pre-central gyrus (FA; von Bonin and Bailey, 1947).

Exps. 2 and 4. Lesions of the middle one-third of the pre-central gyrus (FA).

Exps. 9 and 10. Lesions of the frontal areas (FC, FB), in the former encroaching upon area FA.

Exp. 11. Lesion of the transition zone of areas FB and FA.

Exp. 12. Lesion of the upper one-third of the pre-central gyrus and the caudal strip of the middle one-third of this gyrus (FA).

Exp. 20. Lesion of the lower one-third of the pre-central gyrus (FA, FBA) (Kuypers, 1958*d*).

B. *Post-central and Parietal Lesions*

Exp. 6. Lesion of the entire post-central gyrus (PB, PC encroaching upon PEm, PF).

Exps. 5 and 8. Lesions of the lower two-thirds of the post-central gyrus (PB, PC).

Exp. 7. Lesion of the lower one-third of the post-central gyrus (PB, PC, encroaching upon PF).

Exp. 13. Lesion of the caudal half of the post-central gyrus (PC encroaching upon PEm, PF).

Exps. 14, 15 and 16. Lesions of the superior parietal lobule (PE, PEm).

Exps. 17, 18 and 19. Lesions of the inferior parietal lobule caudal two-thirds (PG, PF).

RESULTS

I. *Lesions of the Pre-central and Frontal Areas* (FA, FB, FBA, and FC)

A. *Pre-central gyrus.*—Following lesions of the upper (Exp. 1) and middle one-third of the pre-central gyrus (Exp. 2) respectively, numerous degenerating fibres descended through the medial cortical bundles of the pons into the pyramidal tract and through the pyramidal decussation and the lateral corticospinal tracts into the spinal cord, predominantly contralateral to the lesion. Degenerating fibres terminated massively in the medial and dorsomedial parts of the pontine nuclei. At pontine and medullary levels only few degenerating fibres distributed to the magnocellular medial tegmental regions (cf. Olszewski and Baxter, 1954), while hardly any such fibres reached the parvicellular lateral tegmentum. However, in both cases a good many degenerating fibres terminated in the magnocellular parts of the cerebellipetal lateral reticular nucleus of the medulla oblongata, where in each of the experiments the degenerating fibres seemed to occupy a slightly different position.[1] Moreover, following the lesion of the upper one-third of the pre-central gyrus, fibre degeneration was observed in the territory of the nucleus gracilis especially its basal and central parts, comprising longitudinally oriented fibres. A great many of these fibres seemed to terminate outside the main cell clusters of this nucleus, while relatively few penetrated them. Since these degenerating fibres could be traced from the pyramidal bundles immediately distal to the decussations, it was inferred that this projection is established predominantly by recurrent pyramidal fibres. This could be confirmed in an additional experiment with the brain-stem cut sagittally. Following the lesion of the middle one-third of the pre-central gyrus (Exp. 2) a similar fibre degeneration was encountered in and around the base of the contralateral cuneate nucleus.

Throughout the entire spinal cord some degenerating fibres distributed to the contralateral zona intermedia and the basal parts of the posterior

[1]The fibres of the upper one-third of the pre-central gyrus to the magnocellular part of the lateral reticular nucleus seem to originate primarily from the medial aspect of the hemisphere and the adjacent parts of the lateral surface.

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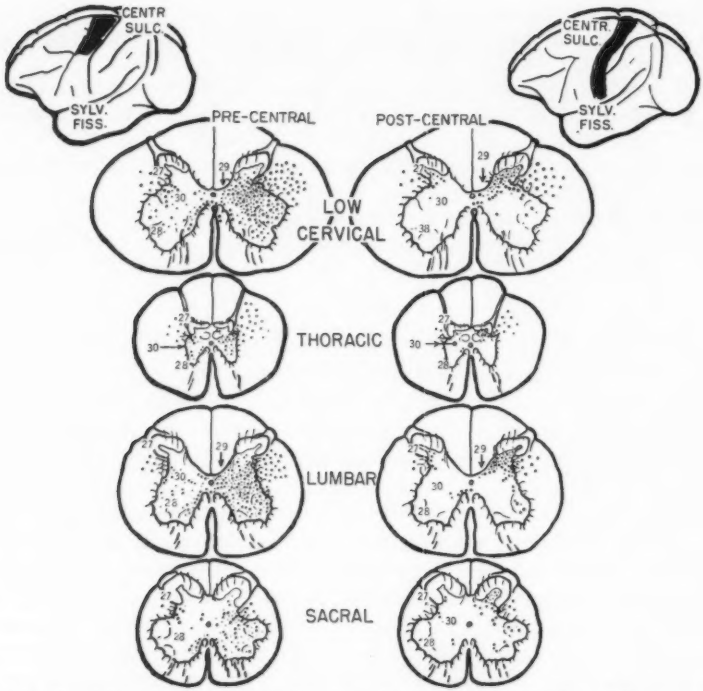

FIG. 2.—Semidiagrammatic approximation of the spinal distribution of degenerating fibres and end-ramifications, following pre-central and post-central lesions respectively. Heavy dots represent degenerating nerve fibres, fine dots represent degenerating end-ramifications. For Key to numbering of text figures see end of article.

horn as well as to the medial parts of both anterior horns (fig. 2).[1] In the case with damage to the upper one-third of the pre-central gyrus, the bulk of the degenerating fibres terminated in the lumbar and sacral regions, distributing to the zona intermedia and the basal parts of the posterior horn as well as to the medial parts of both anterior horns and the lateral part of the contralateral anterior horn.[2] On the other hand, in case of the lesion of the middle one-third of the precentral gyrus, the bulk of the degenerating fibres distributed to the cervical regions of the spinal cord following a similar termination pattern. In both experiments

[1]Relatively little attention has been paid to the location of the descending bundles in the spinal funiculi.

[2]In this as well as in the other experiments, the degenerating elements in the zona intermedia and the basal parts of the posterior horn were more numerous than those in the anterior horn.

hardly any degenerating fibres were encountered in the nucleus proprius of the posterior horn.

In two additional experiments (Exps. 3 and 4) with the lesions likewise involving the upper and middle one-third of the pre-central gyrus, only the brain-stem and cervical spinal cord were available for study. A similar distribution of degenerating elements was observed as in Exps. 1 and 2.

In Case 12, the lesion involved the upper one-third of the pre-central gyrus but additionally damaged the caudal strip of the middle one-third of this gyrus (fig. 1). Degenerating corticospinal fibres distributed in the same fashion as observed following lesions of the upper one-third of the gyrus. At low cervical levels, however, the degenerating fibres in the zona intermedia and the basal parts of the posterior horn were more numerous and some additional degenerating fibres terminated at low cervical levels in the extreme lateral cell groups of the contralateral anterior horn. This latter projection was notably absent following lesions of the upper one-third of the pre-central gyrus.

These findings led to the following conclusion. The upper two-thirds of the *precentral gyrus* project mainly to the *pontine nuclei*, the cerebellipetal *lateral reticular nucleus* of the medulla oblongata and the territories of the *nuclei cuneatus and gracilis*. The corticospinal projection terminates in the *zona intermedia* and the *basal parts of the posterior horn* as well as the medial parts of *both anterior horns* and the *lateral part of the contralateral anterior horn*. The precentral *leg area* projects primarily to the *nucleus gracilis* and the *lumbar spinal segments*, while the pre-central *arm area* projects primarily to the *nucleus cuneatus* and the *low cervical levels* of the spinal cord. The most lateral cell groups of the anterior horn receive a projection arising in the caudal parts of the pre-central gyrus.

B. *Frontal and adjacent parts of the pre-central area.*—On the basis of the findings in three additional experiments (9, 10, 11) with involvement of primarily (fig. 1) the frontal areas (FC, FB) the rostral border of the pre-central projection could be approximated.

In Case 9, the lesion involved frontal areas (FC, FB) while encroaching upon the rostral parts of the pre-central area (FA). The medial parts of the hemisphere and the adjacent white matter were at most peripherally involved. Degenerating cortical fibres descended through the most medial bundles of the pons, the pyramidal tract and the pes lemnisci (Déjerine, 1901). However, only few of the fibres reached the spinal cord. Along this trajectory fibre termination took place in the pontine nuclei (extreme medial parts and the processus supralemniscalis pontis) as well as in the medial pontine tegmentum, especially the ventral parts (fig. 3A, B). The latter distribution field was limited laterally by the nucleus subcoeruleus (Olszewski and Baxter, 1954). A similar distri-

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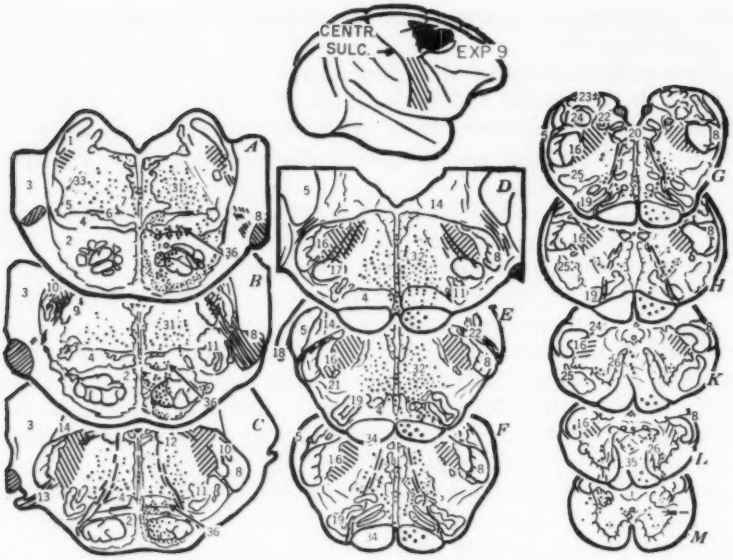

FIG. 3.—Semidiagrammatic approximation of the distribution of degenerating nerve fibres and end-ramifications (symbols as in fig. 2) in the lower brain-stem, as observed in experiment 9. The lateral tegmental areas, receiving cortical fibres from the pre-central face area, are indicated by shading.

bution prevailed in the medulla oblongata, with a good many fibres terminating almost exclusively in the magnocellular medial tegmentum (fig. 3C, D, E). Caudalwards, these fibres rapidly decreased in number, limited as they were to the reticular cells immediately dorsal to the inferior olives. The few corticospinal fibres terminated primarily in the contralateral zona intermedia and the basal parts of the posterior horn throughout the spinal cord, while few additional fibres passed to the medial parts of both anterior horns.

In Case 10, a similar lesion was made, however, without involvement of the pre-central region (FA). The distribution of cortical fibres resembled that found in Case 9, but the fibres to the medullary tegmentum seemed to be less numerous and no degeneration was encountered in the pes lemnisci. The spinal distribution was almost entirely lacking.

In Case 11, the lesion extended parallel to the central sulcus involving the transition zone between the frontal (FB) and the pre-central regions (FA). The degeneration resembled that found in Case 9. The spinal distribution, however, was much more pronounced but followed the same general distribution pattern.

These findings led to the following conclusion. The posterior border of

the lesion in Case 10 corresponds approximately to the rostral border of the corticospinal projection systems, the rostral components of which distribute primarily to the zona intermedia and the basal parts of the posterior horn, while very few additional cortical fibres distribute to the nerve cells in the most medial parts of the anterior horn. Moreover, the rostrally adjacent *frontal areas* (FC, FB) constitute an important source of projections to the *medial pontine and medullary tegmentum*. In this system a topical organization might exist, with the bulk of the corticomedullary projections originating primarily in the caudal parts.

II. *Lesions of the Post-central and Parietal Regions* (PB, PC, Pem, PE, PF, PG)

In order to compare post- and pre-central projections, in Cases 5, 6, 7, 8, 13, 14, 15, 16, 17 and 18 lesions were made involving the post-central and parietal areas (fig. 1).

A. *Post-central gyrus.*—Following a lesion of the entire post-central gyrus (Exp. 6) degenerating fibres descended through the central and lateral pontine bundles into the lateral parts of the pyramidal tract and from there through the pyramidal decussation and the contralateral lateral corticospinal tract into the spinal cord. Fibre termination took place in the pontine nuclei and the territories of the somato-sensory nuclei (fig. 4). Some additional fibres, very limited in number, distributed to spinal motor neurons.

The termination area in the pontine nuclei involved a zone encircling the cortical bundles ipsilateral to the lesion. The projection to the trigeminal sensory nuclei was primarily contralateral and first of all involved the spinal trigeminal complex, slightly less heavy in the dorsomedial subdivision of its middle one-third. The substantia gelatinosa of the trigeminal complex hardly received any cortical fibres. This distribution is in marked contrast to that found in the pre-central experiments (e.g. Case 20; Kuypers, 1958*d*) which exhibited a pronounced degeneration in the parvicellular lateral tegmentum while the adjacent spinal trigeminal complex hardly received any degenerating fibres. Degenerating post-central fibres were present in the territory adjoining the main cell clusters of the principal sensory nucleus of the trigeminus, but very few such fibres appeared to penetrate them. Rostralwards, these fibres gradually decreased in number and were almost lacking around the rostral pole of the nucleus. This distribution is notably in contrast to that found in the pre-central experiments (e.g. Exp. 20, Kuypers, 1958*d*) in which some degenerating fibres distributed in the same fashion but the majority projected to the dorsolateral parts of the tegmentum (nucleus supratrigeminalis of Lorente de Nó, 1933). The trajectory along which the post-central fibres reached the trigeminal nuclei was difficult to determine. Relatively few fibres reached the nuclei transtegmentally.

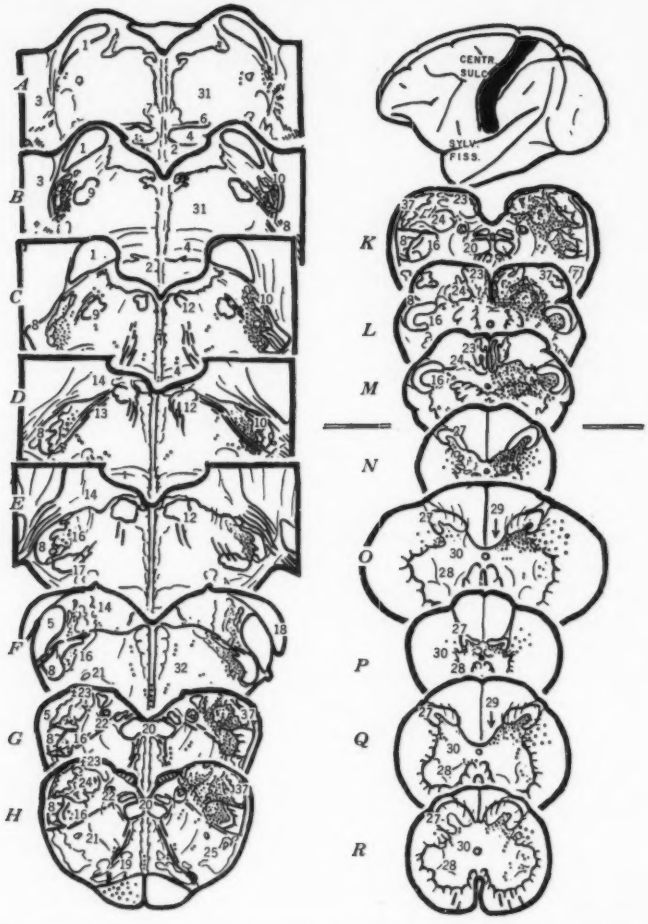

FIG. 4.—Semidiagrammatic approximation of the distribution of degenerating nerve fibres and end-ramifications, following a lesion of the post-central gyrus (symbols as in fig. 2).

On the other hand, at the base of the trigeminal complex many degenerating longitudinal fibres were observed, constituting the immediate source of the projections to this nucleus. Some recent findings indicate that these fibres possibly form a recurrent bundle, but a massive continuity with the pyramidal tract as yet could not be established. Similar to the findings in the pre-central experiments (Exps. 1, 2, 3, and 4) degenerating pyramidal fibres out of the decussation passed dorsally to the region of

the nuclei cuneatus and gracilis. The fibres to the region of the nucleus cuneatus were more numerous than observed following pre-central lesions. Part of the degenerating fibres subsequently followed a longitudinal trajectory and could be traced along the entire length of the nuclei, grouped together in the area dorsolateral to the solitary tract. From this area degenerating fibres penetrated the territory of the nuclei forming two distinct bundles, passing laterally (fig. 4G, H, K) on both sides of the pars rotunda of the cuneate nucleus (Ferraro and Barrera, 1935). Similar to previous findings in the caudal parts of the nucleus gracilis, relatively few degenerating elements seemed to ramify within the main cell clusters of these nuclei and a great many seemed to terminate in the immediate vicinity of the cell nests.

The post-central spinal projection reached its destination primarily through the contralateral lateral corticospinal tract. At all levels of the spinal cord, from this tract numerous degenerating fibres of small calibre entered the spinal grey matter and terminated in the nucleus proprius[1] and the internal basal parts of the posterior horn (nucleus of the spinal posterior commissure). Hardly any fibres reached the substantia gelatinosa. Only very few degenerating fibres terminated in the zona intermedia and the external basal parts of the posterior horn, in contrast to the findings in the pre-central experiments (fig. 2). In addition, at low cervical and lumbar levels a very limited number of degenerating fibres contacted motor neurons, almost exclusively those in the lateral parts of the contralateral anterior horn (fig. 4).

In the remaining cases of lesions covering different parts of the post-central gyrus, largely similar distributions were observed. In Cases 5 and 8, with lesions involving the lower two-thirds of the post-central gyrus, degenerating elements were most numerous in the sensory trigeminal nuclei, the dorsal grey matter in the upper and lower cervical regions and the region of the nucleus cuneatus. In Experiment 7, with the lesion involving the lower one-third of the post-central gyrus the degenerating elements were almost entirely limited to the trigeminal sensory nuclei.

In order to detect differential projections from the rostral and caudal parts of the post-central gyrus, a lesion was made involving its posterior half (Exp. 13). In this experiment, as compared with a lesion of the entire gyrus (Exp. 6) the degenerating fibres were less numerous, but no obvious differences in distribution could be observed. The degenerating fibres distributing to the thoracic spinal grey matter seemed slightly more numerous than following lesions of the lower two-thirds of this gyrus (Exps. 5 and 8).

[1]A comparison with the findings in the pre-central experiments indicated a slight overlap of the pre-central termination area into the ventral parts of this post-central termination area, most pronounced in the internal basal parts of the posterior horn.

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The total of these findings led to the following conclusion. The *post-central gyrus* projects to the territories of the *main sensory nucleus of the trigeminus* and the *nuclei cuneatus and gracilis*. Moreover it sends fibres to the *spinal trigeminal complex* as well as the *nucleus proprius* and the adjacent *internal basal parts* of the *spinal posterior horn*. Furthermore, few post-central fibres distribute to the cells in the *lateral parts of the spinal anterior horn*. The fibres to the sensory nuclei of the trigeminus originate primarily in the lower one-third of the post-central gyrus. The fibres to the nucleus cuneatus and the cervical spinal segments arise primarily in the middle one-third, while the fibres to the nucleus gracilis and the lumbar segments of the spinal cord arise primarily in the upper one-third of the post-central gyrus.

B. *Parietal regions.*—On the basis of the findings in Cases 14, 15, 16, 17, 18 and 19 the caudal border of the field of origin of the post-central projections could be determined.

(1) Superior parietal lobule: Following two lesions involving the dorsal parts of the superior parietal lobule (Pem, PE; Exps. 14 and 16) degenerating fibres descended through the lateral pontine bundles and the pyramidal tract into the spinal cord. Along this trajectory fibres terminated in the lateral parts of the pontine nuclei. In the lower brain-stem some degenerating fibres distributed to the territory of the nucleus gracilis. The fibres which descended into the spinal cord distributed mainly to the lumbar regions, where a small but discrete bundle of degenerating fibres was found to pass to the internal basal parts of the posterior horn and the nucleus proprius, contralateral to the lesion. Very few additional fibres appeared to terminate in the zona intermedia. In Experiment 15 the lesion involved the entire superior parietal lobule (PEm, PE). In this case likewise a limited number of degenerating fibres distributed to the nucleus gracilis and the lumbar segments of the spinal cord, but in addition a similar small but distinct projection was encountered distributing to the territory of the nucleus cuneatus and the dorsal grey matter of the cervical segments of the spinal cord.

(2) Inferior parietal lobule: Following a lesion involving the posterior two-thirds of the inferior parietal lobule (PF, PG; Exp. 17) only a sporadic degenerating fibre was encountered in the lower brain-stem and the spinal cord. Peele (1942), however, reported a projection from this area to the cervical spinal cord. As a consequence two additional lesions were made involving the inferior parietal lobule (Exps. 18 and 19). In neither of these two cases could a discrete group of degenerating fibres be observed passing either to the nuclei gracilis and cuneatus or to the spinal grey matter. Only in Case 19 some scattered degenerating fibres were observed in the lumbar region. The appearance of this degeneration, however, suggested a much longer standing than could be accounted for by the

eleven days' survival period. In view of the possibility of pre-existing pathology, this solitary finding has been discounted.

The total of these findings regarding the parietal area led to the following conclusions. *Only the superior parietal lobule* contributes to the *corticobulbar* and *corticospinal projections*. The upper part of the superior parietal lobule projects primarily to the nucleus gracilis as well as to the nucleus proprius and the mediobasal parts of the posterior horn in the lumbar segments. The lower parts of this parietal area project in a similar fashion to the spinal grey matter at cervical levels and to the cuneate nucleus. At these spinal levels very few additional fibres terminated in the zona intermedia. Since in none of the experiments area PE was involved exclusively, it could not be decided whether or not area PE by itself contributes to this projection.

Survey of the Present Findings

Projection systems in general can be grouped among others either on the basis of their origin, or on the basis of their termination. Previous studies tended to group the cortical projections according to their origin, by posing the question: What fibres originate in a given cortical area and where do they terminate? On the other hand, since the function of the higher levels of the neural apparatus ultimately will have to be understood in terms of their relation with segmental apparatus, a grouping of the projection systems on the basis of their termination was thought to be the most promising approach. However, such a classification requires detailed knowledge of the organization of the segmental apparatus. Since the available data pertinent to this organization are as yet incomplete, grouping according to termination encounters some difficulties. On the other hand, obvious differential patterns in the termination of the cortical projections appeared to make some such difficulties surmountable.

Spinal internuncial elements, relaying impulses to the anterior horn cells (Cajal, 1909) are located in the intermediate region and the external basal parts of the posterior horn (Lloyd, 1941*b*; Bernhard and Rexed, 1945). The cells in these regions received a projection originating primarily in the pre-central gyrus (FA) with possible additional contributions from adjacent caudal parts of the area FB (fig. 5.·.). Only few such fibres arise from the post-central and superior parietal areas (PB, PC, PEm, PE?). The literature is inconclusive regarding the precise dorsal border of this internuncial area. We have *arbitrarily* accepted as such the rather sharp line demarcating the posterior horn proper against the accumulation of degenerating elements in the intermediate region and the external basal parts of the posterior horn observed following extensive pre-central lesions (Plate XXVIII). This border corresponds

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approximately to that found by electrophysiological methods (Bernhard and Rexed, 1945).

The cell population of this "internuncial" region continues into the parvicellular lateral pontine and medullary tegmentum. The findings of Lorento de Nó (1922, 1933) and M. E. Scheibel (1955) suggest that at least some of the cells in this region represent similar internuncial elements. This lateral tegmental region, as also its presumable spinal homologue, receives primarily pre-central projections, specifically from the lower one-third (fig. 3, fig. 5.·.) of the pre-central gyrus (Kuypers, 1958*d*).

The cortical field projecting to the internuncial elements approximately coincides with the field of origin of *cortico-motoneuronal* projections, the bulk of which originates in the pre-central gyrus (fig. 5■) with some post-central contributions. Those components of this projection which

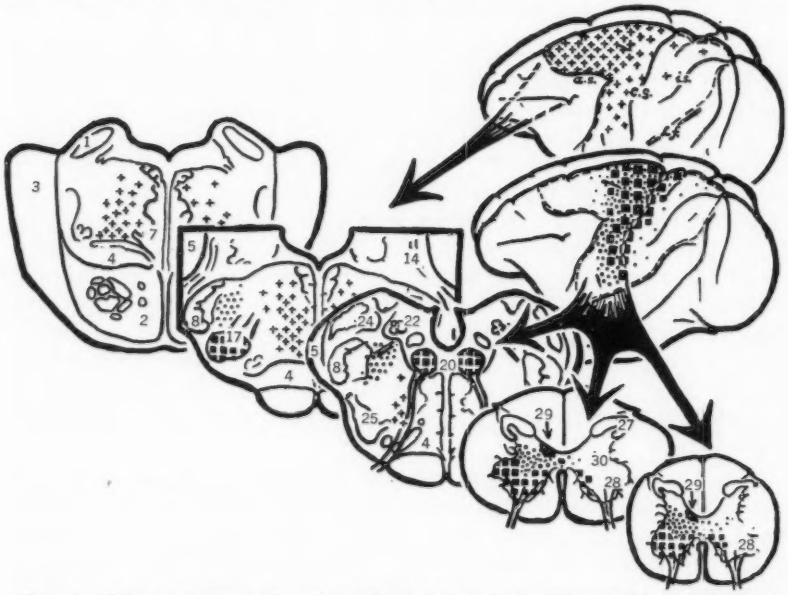

FIG. 5.—Diagram illustrating the differential cortical origin of the projections to the medial pontine and medullary tegmentum ($_{+}{}^{+}{}_{+}$); the spinal intermediate region, etc., and the lateral tegmentum of the lower brain-stem (·.·); and cranial motor nuclei and the spinal anterior horn (■). The projections to the medial parts of both anterior horns might not be cortico-motoneuronal in nature. Laterality has been omitted.

articulate with the most lateral motor neurons in the spinal anterior horn arise primarily from the caudal parts of this field: the caudal parts of the pre-central gyrus and the post-central gyrus. The fibres distributing

to the medial parts of both anterior horns have a more diffuse origin. Moreover the nature of these fibres might be cortico-internuncial rather than cortico-motoneuronal (cf. Sprague, 1951).

The medial parts of the *pontine and medullary tegmentum* contain *reticular cell groups* which, contrary to the parvicellular lateral reticular elements, project rostrally (Kohnstamm and Quensel, 1908*a*, *b*; Brodal and Rossi, 1955; M. and A. Scheibel, 1958; Nauta and Kuypers, 1958) and caudally (e.g. Kohnstamm, 1899; Papez, 1926; Torvik and Brodal, 1957) beyond these brain-stem segments. These reticular cells (Torvik and Brodal, 1957) are the recipients of a third cortical projection, the bulk of which originates in frontal regions (FC, FB; fig. 5_{+}^{+}) with some pre-central contribution. The present findings suggest the possibility of a topical organization in this cortico-reticular projecting, with the bulk of the cortico-medullary projections originating somewhat caudally.

Previous descriptions (Kohnstamm and Quensel, 1908; Cajal, 1909; Bok, 1928; and others) suggest that the rostrally projecting *secondary sensory elements* of the *spinal cord* are located in the nucleus proprius of the posterior horn. These cells are the recipients of a fourth cortical projection system, the bulk of which originates post-centrally, with some additional contributions from the superior parietal lobule (PB, PC, PEm and PE?) and only very few from the pre-central gyrus (fig. 6).

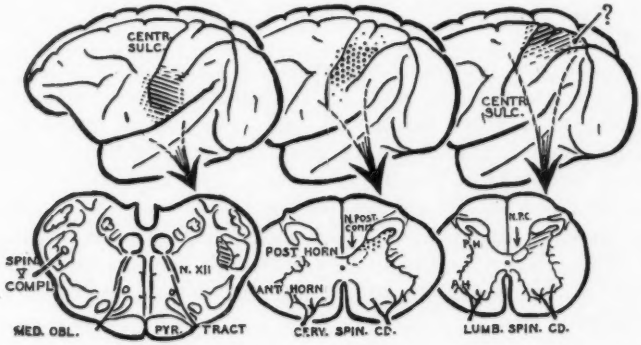

FIG. 6.—Diagrammatic approximation of the cortical origin of the nerve fibres projecting to the spinal trigeminal complex and the region of the nucleus proprius in the low cervical and lumbar segments of the spinal cord.

The territory of the *epicritic sensory nuclei cuneatus and gracilis* constitutes the terminal region of a fifth cortical projection. A great many of these fibres seem to tend to terminate outside the main cell clusters of these nuclei, best demonstrable in parts of the nucleus gracilis. This projection arises from the pre-central gyrus, the post-central gyrus and the superior parietal lobule (fig. 7). The epicritic function of the

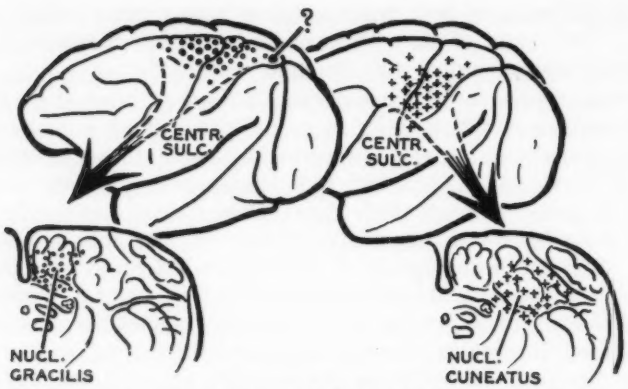

FIG. 7.—Diagrammatic approximation of the cortical origin of the nerve fibres projecting to the region of the nuclei cuneatus and gracilis respectively.

principal sensory nucleus of the trigeminus places the cortical projection to the region of this nucleus in the same category. Notably, a great many fibres of this projection likewise tend to terminate outside the main cell clusters of this nucleus. The cortical origin is difficult to determine, for the region of this nucleus is somewhat less than well defined. The present findings suggest a primarily post-central origin with some pre-central contributions.

Finally a cortical projection to the cells of the *mediobasal parts* of the *posterior horn was observed* (figs. 2, 5). It is mentioned separately since these fibres arise from pre-central and post-central territories, thus resembling the projection to the region of the nuclei cuneatus and gracilis. The spinal recipients of this projection are in all likelihood the cells of the internal basal nucleus (nucleus of the spinal posterior commissure), at least some of the axons of which ascend in the posterior funiculus (Cajal, 1909). Since the function of these cells appears to be unknown the place of this projection among the corticofugal systems is difficult to determine.

DISCUSSION

The present findings in general tend to agree with the data available in the literature.

A. Cortical projections to the *medial reticular cell groups* of the *pontine* and *medullary tegmentum* have been observed in the monkey (Simpson and Jolly, 1907; Mettler, 1935, 1947; Levin, 1936; Verhaart and Kennard, 1940; Hines, 1943; Krieg, 1954). However, outstanding quantitative differences between the pre-central and frontal contributions were not emphasized. Similar quantitative differences were encountered in the cat (Kuypers, 1958*a*). Somewhat in agreement with McCulloch *et al.*

(1946) and Peterson and Brickers (1952) the present findings suggest that the corticomedullary components might arise especially from an area immediately rostral to the pre-central gyrus although originating also in more rostral parts (FB and FC).

B. *Pre-central corticospinal fibres* have long been commonly accepted. Sherrington (1890) and Mellus (1899) observed them in primates and von Monakow (1886) suggested the intermediate region as their termination area. The additional termination in the anterior horn in primates, observed in the present study, was noticed by Sherrington (1890) and Déjerine and Déjerine (1904) and confirmed by Hoff and Hoff (1934), Bernhard and Bohm (1954), and Chambers and Liu (1958).

The rostral border of this cortical projection field in terms of cyto-architecture is still somewhat controversial. The present observations indicate that the trunk area of Woolsey *et al.* (1952) still contributes some fibres to these corticospinal projections, in marked contrast to the rostrally adjacent frontal areas (FC and FB).

C. *Post-central corticospinal* fibres initially noticed among others by Mellus (1894), Sachs (1909) and Vogt and Vogt (1919) were found to be of small diameter (Vogt and Vogt, 1919; Lassek, 1952), which agrees with the present observations. Contrary to the findings of Sakuma (1937) and those of the present study, Peele (1942) traced a distinct corticospinal (cervical) projection from area 7 (PF, PG). His one and only lesion in this area, however, clearly encroached upon area 5 (PEm, PE), which in the present study was found to project to the cervical region.

Although the existence of post-central corticospinal projections was recognized, the preferential distribution to the nucleus proprius and the internal basal parts of the posterior horn has not been reported. However, in general, cortical fibres to the secondary sensory nuclei have been observed by Torvik (1956), Brodal *et al.* (1956), Kuypers (1956, 1958*a*, *b*, *d*), and Chambers and Liu (1957, 1958).

D. Cortical fibres to the region of the *nuclei cuneatus and gracilis* were first noticed by Redlich (1897) in the cat. More recently Walberg (1957), Chambers and Liu (1957) and the present author (1956, 1958*a*) studied them in more detail. The existence of similar fibres in man has also been reported (Kuypers, 1958*b*).

The present findings invite a comparison with data obtained by stimulation of these cortical areas. Since Grünbaum and Sherrington (1901) and Leyton and Sherrington (1917), the pre-central gyrus has been considered to represent the "motor cortex." More recent studies (Woolsey *et al.*, 1952) demonstrated that distal movements are primarily obtained from the more caudal parts in close proximity of the central sulcus, while proximal movements are elicitable primarily from a rostrally adjoining zone. This rostro-caudal organization finds an anatomical counterpart in the reported pattern of the cortico-motoneuronal connexions. The

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projections to the lateral cell groups of the anterior horn, believed to innervate the distal extremity musculature (cf. Kappers *et al.*, 1936; Bok, 1928; Pollak, 1935; Sprague, 1951), were found to originate primarily around the central sulcus (pre- and post-central gyri).

Furthermore, pre-central corticospinal fibres distribute to the internuncial elements, connected with the motor neurons (Cajal, 1952; Lloyd, 1941*b*; Bernhard and Rexed, 1945). These fibres likely represent an indirect cortico-motoneuronal pathway, paralleling the direct cortico-motoneuronal connexions. In the rostral part of the pre-central motor cortex (Woolsey *et al.*, 1952) these indirect cortico-motoneuronal connexions seemed to become relatively more dominant since the fibres to the motor neurons are drastically reduced. This holds true especially if the magnocellular elements in the medial parts of the anterior horn represent propriospinal elements rather than motor neurons (Sprague, 1951). Regarding a rostral dominance of the cortico-internuncial connexions, similar observations were made in the pre-central face area (Kuypers, 1958*d*).

This increase in dominance of the indirect cortico-motoneuronal connexions is accompanied by an increase in projections to the medial reticular cell groups of the pontine and medullary tegmentum, which give rise to reticulospinal fibres (Torvik and Brodal, 1957) influencing spinal segmental apparatus (Lloyd, 1941*a*; Magoun and Rhines, 1946; Niemer and Magoun, 1947) especially important for posture (Sprague and Chambers, 1954). This suggests that the cortico-medullary projection, an important projection in the trunk area (Woolsey, *et al.*, 1952) constitutes a cortical connexion with bulbar postural mechanisms, representing a second category of polysynaptic cortico-motoneuronal connexions.

In other words, the more rostral a "point" in the "motor cortex" the more likely its stimulation, following Woolsey *et al.* (1952), will elicit proximal movements and as an anatomical corollary, the more polysynaptic the cortico-motoneuronal relation, involving spinal internuncial cells as well as brain-stem reticular elements. Such a concept forms the anatomical counterpart of that brought forward by Bernhard and Bohm (1954) on the basis of their electrophysiological findings.

The polysynaptic cortico-motoneuronal connexions appear to be especially susceptible to the action of barbiturates, since they interfere primarily with proximal movements obtained from rostral parts of the "motor area" (Bucy, 1933). The rostral increase in pre-central stimulatory threshold under anæsthetic conditions (cf. fig. 123, Woolsey *et al.*, 1952) might thus find its explanation in the increase in number of synapses through which the motor neurons are reached. Furthermore, differences in stimulation frequency likewise were found to affect the stimulatory responses (Liddell and Phillips, 1950; Hyde and Gellhorn, 1951; Cure

and Rasmussen, 1954). A comparison of these results with present findings suggest that different frequencies activate motoneurons along different pathways: "indirect" and "direct" cortico-motoneuronal connexions.

The primarily post-central and superior parietal projections to the nucleus proprius of the spinal cord and the spinal trigeminal complex, can be interpreted as a cortical sensory "feedback" mechanism, since it originates in the receiving area for certain cutaneous sensory modalities (Woolsey *et al.*, 1942) at least in part relayed by the recipients of this projection (Walker, 1940). The concept of such a cortical somatosensory "feedback" mechanism is by no means original, having been brought forward already by Foerster (1927), Wallenberg (1928), Brouwer (1933) and Peele (1942), despite the absence of adequate data. If this concept is correct, the projections to the region of the nuclei cuneatus and gracilis and the principal sensory nucleus of the trigeminus represent a comparable "feedback" different only in respect to the sensory modalities involved. In the Rhesus monkey the cortical receiving area, especially for proprioceptive sensory modalities, seems to extend rostrally into the pre-central region (Minkowski, 1917; Woolsey and Bard, 1936; Penfield and Boldrey, 1937; Kennard and Kessler, 1940; Peele, 1944; Woolsey *et al.*, 1947; Gay and Gellhorn, 1949; Malis *et al.*, 1953 and Adey *et al.*, 1954). If this be accepted, the origin of the projections to the nucleus cuneatus and gracilis appears to be identical with the receiving area for proprioceptive and related sensory modalities, believed to be subserved by these nuclei. Such an identity, likewise encountered in the optic system (Brouwer, 1928; Biemond, 1929, 1930) forms an additional argument in favour of the present concept.

A cortico-somatosensory reciprocity is made likely by Hagbarth and Kerr's (1954) findings of a cortical influence upon the primary sensory synapses in the cat's spinal cord.[1] The occurrence of the "extinction" phenomenon (cf. Bender, 1952; Critchley, 1953) and the release of tactile avoiding reactions (Denny-Brown and Chambers, 1958) prominent after post-central and parietal lesions, might in part be due to the interference with these sensory "feedback" mechanisms.

Prior to the studies of Grünbaum and Sherrington (1901) and Leyton and Sherrington (1907), the post-central and parietal areas were included in the "motor cortex" (Ferrier, 1886; cf. Schäfer, 1900) since stimulation produced motor phenomena. These motor phenomena could still be obtained in the absence of (Kennard and McCulloch, 1943) pre-central and supplementary motor areas (Woolsey *et al.*, 1953); and their topographical pattern parallels that of the sensory representation (Woolsey

[1]The pyramidal nature of the cortical influence upon the nuclei of the posterior funiculus has been demonstrated most recently by: Magni, F.; Melzack, R.; Moruzzi, G.; and Smith, C. (1959) *Arch. ital. Biol.*, **97**, 357.

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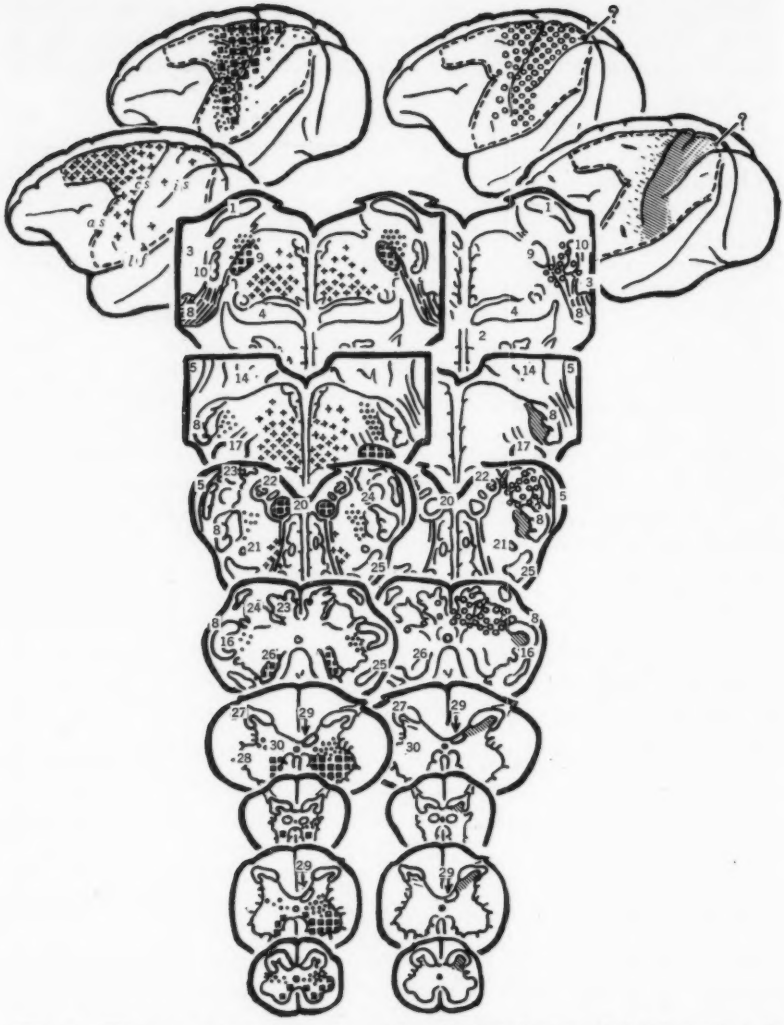

FIG. 8.—Diagram summarizing the origin and distribution of the frontal, pericentral and parietal cortico-bulbar and -spinal projections. The projections to the regions of the sensory nuclei (o°o and ///) are represented in the right column. Projections to the reticular cell groups ($_{+}{}^{+}{}_{+}$), the "internuncial elements" (·-·), and the cranial motor nuclei and the anterior horn (■) are represented in the left column. The projections to the medial part of both anterior horns might not be cortico-motoneuronal in nature. The pre-central and post-central corticospinal projections to the internal basal parts of the posterior horn (29) are omitted in the diagram.

et al., 1942). The motor phenomena find a possible explanation in the limited number of post-central cortico-motoneuronal fibres. However, the high post-central stimulatory threshold (cf. Welker *et al.*, 1957) suggests the involvement of polysynaptic pathways between cortex and motor neurons. The post-central fibres to the region of the nucleus proprius consequently seem to emerge as a likely main route for impulses to these motor neurons, together with the small number of fibres to the zona intermedia and those to the internal basal parts of the posterior horn.[1] Such activation of motor neurons would be possible if the cells in the secondary sensory nuclei entertain connexions with either motor neurons or internuncial elements. Some observations (Cajal, 1952; Bok, 1928; Lorente de Nó, 1933; Lloyd, 1941*b*) suggest this possibility, which would clarify the close correlation between the post-central motor and sensory patterns (Lilly, 1953; Woolsey *et al.*, 1953). However, it implies that motor phenomena might occur merely as a side-product of the stimulation of a system which primarily modified the threshold of cells in the secondary sensory nuclei. This would seriously compromise the conventional notions of "motor cortex" illustrating as it does how the nature and formulations of the experimenter's question is incorporated in the experimental data obtained (cf. Walshe, 1951).

Since the majority of the above described cortical projections are incorporated in the *pyramidal tract*, at least three groups of pyramidal fibres can be distinguished (fig. 8).

(*a*) *Frontal* cortical fibres distributing to the medial *pontine and medullary tegmentum.*

(*b*) Primarily *pre-central* cortical fibres distributing to the cranial and spinal "*internuncial elements*" and *motor neurons*, believed to be involved primarily in motor functions.

(*c*) *Pre-central, post-central and superior parietal* cortical fibres distributing to the region of the *nuclei cuneatus and gracilis* as well as the *nucleus proprius* of the spinal cord, possibly representing sensory "feedback" mechanisms.

Summary

Findings regarding a differential distribution of pre-central and post-central cortical fibres to medullary motor and sensory nuclei, prompted a more general study of the cortical projections to the lower brain-stem and the spinal cord. The data were obtained in 20 Rhesus monkeys by studying the fibre degeneration (Nauta-Gygax silver impregnation technique) following lesions in the frontal, pericentral and parietal areas.

[1]Findings in this spinal region of a high stimulatory threshold for activation of the motor neurons innervating distal musculature (Bernhard and Rexed, 1945) render it less likely that the internal basal parts of the posterior represent a major relay in the parieto-cortico-motoneuronal connexions.

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On the basis of the differential termination of these cortical fibres, the following projection systems could be distinguished. (A) A primarily frontal projection to the reticular cell groups in the pontine and medullary tegmentum. (B) A predominantly pre-central projection to the parvicellular lateral medullary and pontine tegmentum, and the basal parts of the posterior horn and the zona intermedia in the spinal cord. (C) A predominantly pre-central projection to some cranial motor nuclei and the spinal anterior horn. (D) A predominantly post-central and superior parietal projection to the region of the nucleus proprius in the spinal cord and the spinal trigeminal complex. (E) A pre-central, post-central and superior parietal projection to the region of the nuclei cuneatus and gracilis.

Additional projections to the region of the principal sensory nucleus of the trigeminal and the internal basal parts of the spinal posterior horn are discussed. The inferior parietal area does not seem to contribute substantially to any of these projections.

A correlation of the anatomical findings with the physiological data has been attempted.

ACKNOWLEDGMENT

The author wishes to thank Dr. W. J. H. Nauta for his invaluable help and advice; Dr. D. McK. Rioch for the use of the surgical facilities of the Department of Neuro-Psychiatry, Walter Reed Army Institute of Medical Research (Washington, D.C.) and Dr. C. N. Woolsey and Dr. R. B. Livingston for their interest and encouragement.

KEY TO THE NUMBERING OF TEXT FIGURES

1. Brachium Conjunctivum (Superior cerebellar peduncle).
2. Pontine Nuclei.
3. Brachium Pontis (Medial cerebellar peduncle).
4. Medial Lemniscus.
5. Restiform Body (Inferior cerebellar peduncle).
6. Supralemniscal Pontine Process.
7. Papillioform Nucleus.
8. Trigeminal Nerve and Spinal Trigeminal Tract.
9. Trigeminal Motor Nucleus.
10. Principal Trigeminal Sensory Nucleus.
11. Superior Olivary Nucleus.
12. Abducens Nucleus and Abducens Nerve.
13. Facial Nerve.
14. Vestibular Complex.
15. Nucleus of the Lateral Lemniscus.
16. Spinal Trigeminal Complex.
17. Facial Nucleus and Facial Nerve.
18. Cochlear Nuclei and Cochlear Nerve.
19. Inferior Olivary Nucleus.
20. Hypoglossal Nucleus, Hypoglossal Nerve.
21. Nucleus Ambiguus.
22. Solitary Nucleus and Solitary Tract.
23. Nucleus Gracilis.
24. Nucleus Cuneatus.
25. Lateral Reticular Nucleus of the Medulla Oblongata.
26. Supraspinal Nucleus.
27. Posterior Horn of the Spinal Grey Matter.
28. Anterior Horn of the Spinal Grey Matter.
29. Internal Basal Parts of the Spinal Posterior Horn (Nucleus of the Spinal Posterior Commissure).
30. Intermediate Region of the Spinal Grey Matter.

31. Nucleus Reticularis Pontis.
32. Magnocellular Reticular Nucleus of the Medulla Oblongata.
33. Subcoerulear Nuclei.
34. Pyramidal Tract.
35. Pyramidal Decussation.
36. Pes Lemnisci.
37. External Cuneate Nucleus.

a.s. Arcuate Sulcus.
c.s. Central Sulcus.
l.f. Lateral Fissure.
i.s. Intraparietal Sulcus.

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LEGENDS FOR PLATES

PLATE XXVIII

REF. 1.—Composite photomicrograph of the intermediate region and the posterior horn of the lumbar spinal cord, following pre-central lesion (Case 12). Note the abundance of degenerating fibres, almost entirely limited to the basal parts of the posterior horn and the zona intermedia. Silver impregnation following the Chambers and Liu (1956) modification of the Nauta-Gygax (1954) technique. $\pm \times 160$.

REF. 2.—Semidiagrammatic representation of the distribution of degenerating elements in ref. 1.

PLATE XXIX

REF. 3.—Composite photomicrograph of the intermediate region and the posterior horn of the lumbar spinal cord following post-central lesion (Case 6). Note the degenerating elements in the region of the nucleus proprius and the internal basal parts of the posterior horn. Silver impregnation as above. $\pm \times 160$.

REF. 4.—Semidiagrammatic representation of the distribution of degenerating elements in ref. 3.

REF. 5.—Photomicrograph of degenerating elements in the intermediate region of the lumbar spinal grey matter, following pre-central lesion (Case 12). Detail of ref. 1. Silver impregnation as above. $\pm \times 500$.

REF. 6.—Photomicrograph of degenerating elements in the region of the nucleus proprius and the internal basal parts of the posterior horn following post-central lesion (Case 6). Detail ref. 3. Impregnation as above. $\pm \times 500$.

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PLATE XXX

REF. 7.—Photomicrograph of large motor neuron in the lumbar spinal cord, following pre-central lesion (Case 12). Note degenerating end-ramifications in contact with the surface of the nerve cell body. Characteristics of degeneration are most obvious in the left fibre, while less convincing in the right fibre. Impregnation as above. ± × 600.

REF. 8.—Photomicrograph of a larger nerve cell in the region of the nucleus proprius of the lumbar spinal cord, following post-central lesion (Case 6). Note the presence of two degenerating end-ramifications (arrows). Impregnation as in ref. 1. ± × 1100.

REF. 9.—Photomicrograph of a cell cluster in the caudal part of the principal sensory nucleus of the trigeminus. Cresyl violet ± × 150.

REF. 10.—Photomicrograph of the degenerating elements in close proximity of the caudal parts of the principal sensory nucleus of the trigeminus, following post-central lesion (Case 7). Note the sparsity of degenerating elements in the cell cluster of the principal sensory nucleus of the trigeminus. Impregnation as above. ± × 200.

REF. 11.—Photomicrograph of the parvicellular lateral tegmentum of the lower medulla oblongata, following post-central lesion. Note the absence of degenerating elements. Impregnation as above. ± × 500.

REF. 12.—Photomicrograph of the spinal trigeminal complex in the lower medulla oblongata, following post-central lesion (Case 6). Note the presence of degenerating elements (cf. lateral tegmentum, ref. 11). Impregnation as above. ± × 500.

REF. 13.—Photomicrograph of degenerating fibres curving over the pars rotunda of the nucleus cuneatus, as observed following a post-central lesion (Case 6). Impregnation as above. ± × 500.

REF. 14.—Photomicrograph of degenerating fibres curving around the lateral side of the pars rotunda of the nucleus cuneatus, as observed following a post-central lesion (Case 6). Impregnation as above. ± × 500.

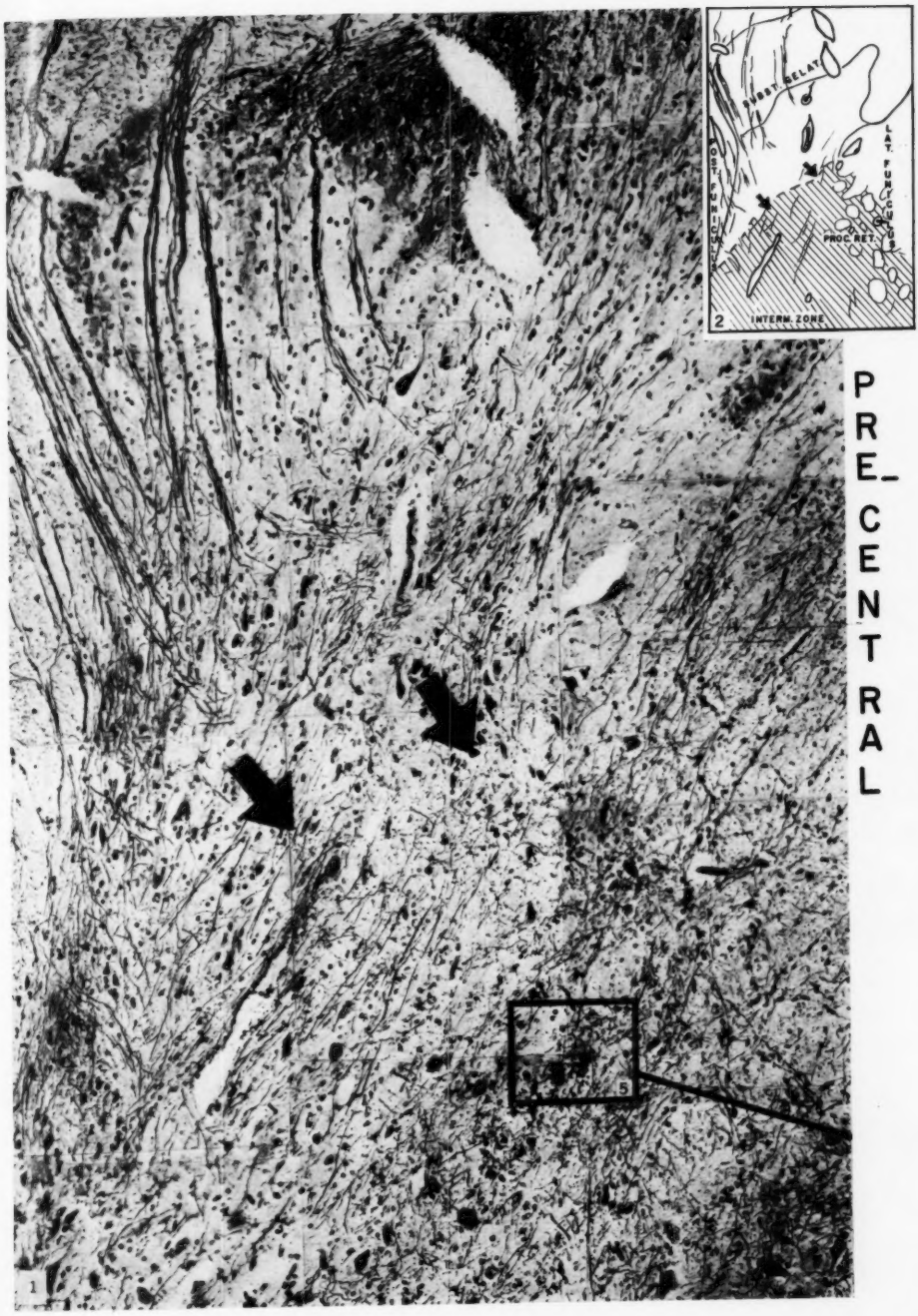
PLATE XXXI

REF. 15.—Photomicrograph of a part of the spinal trigeminal complex following pre-central lesion (Case 20). Note the absence of degenerating elements. ± × 1000.

REF. 16.—Photomicrograph of a part of the parvicellular lateral medullary tegmentum, following pre-central lesion (Case 20). Note the presence of degenerating elements. ± × 1100.

REF. 17.—Photomicrograph of a part of the spinal trigeminal complex, following post-central lesion (Case 7). Note the presence of degenerating elements. ± × 1000.

REF. 18.—Photomicrograph of a part of the parvicellular lateral medullary tegmentum, following post-central lesion (Case 7). Note the absence of degenerating elements. ± × 1000.



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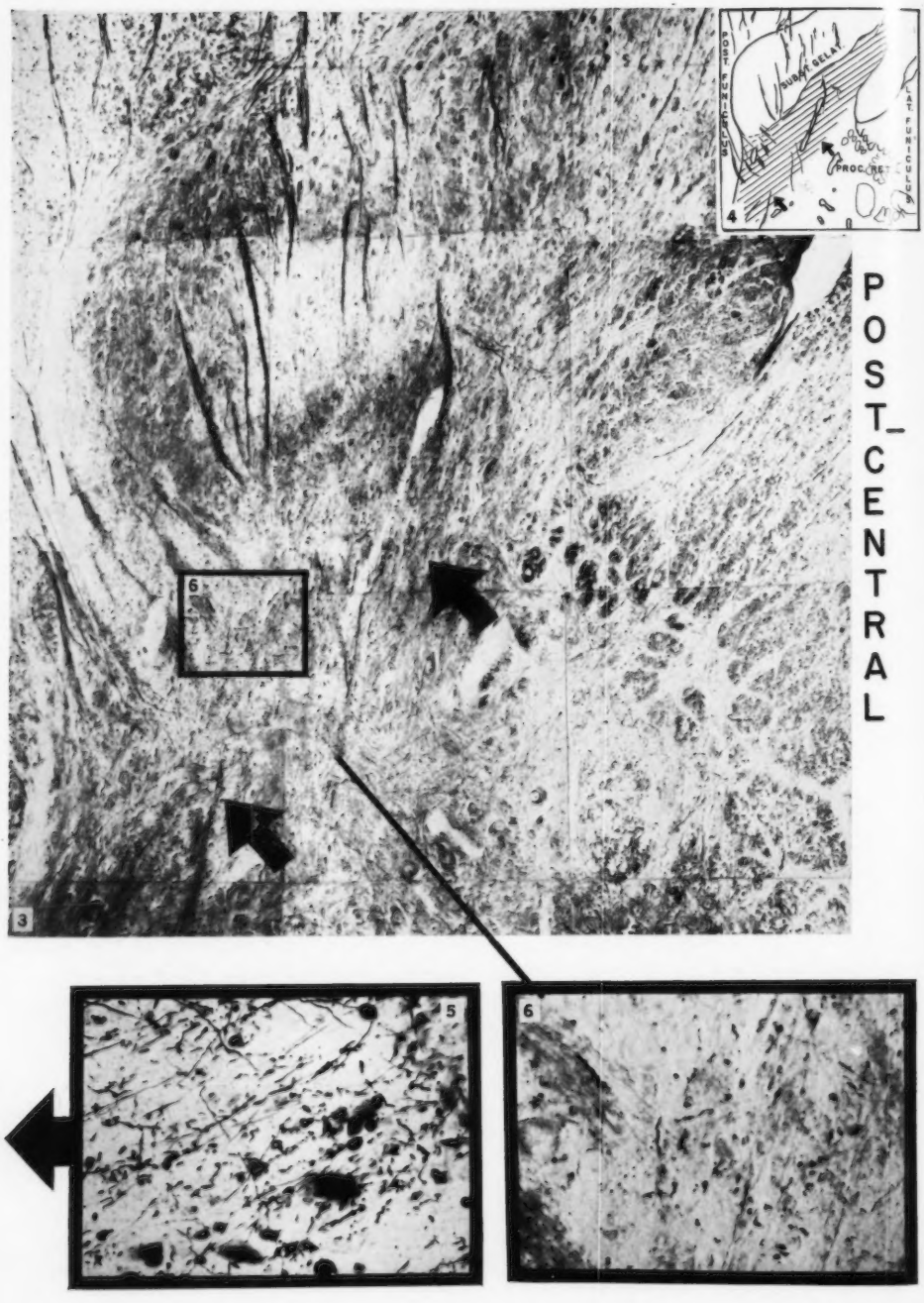

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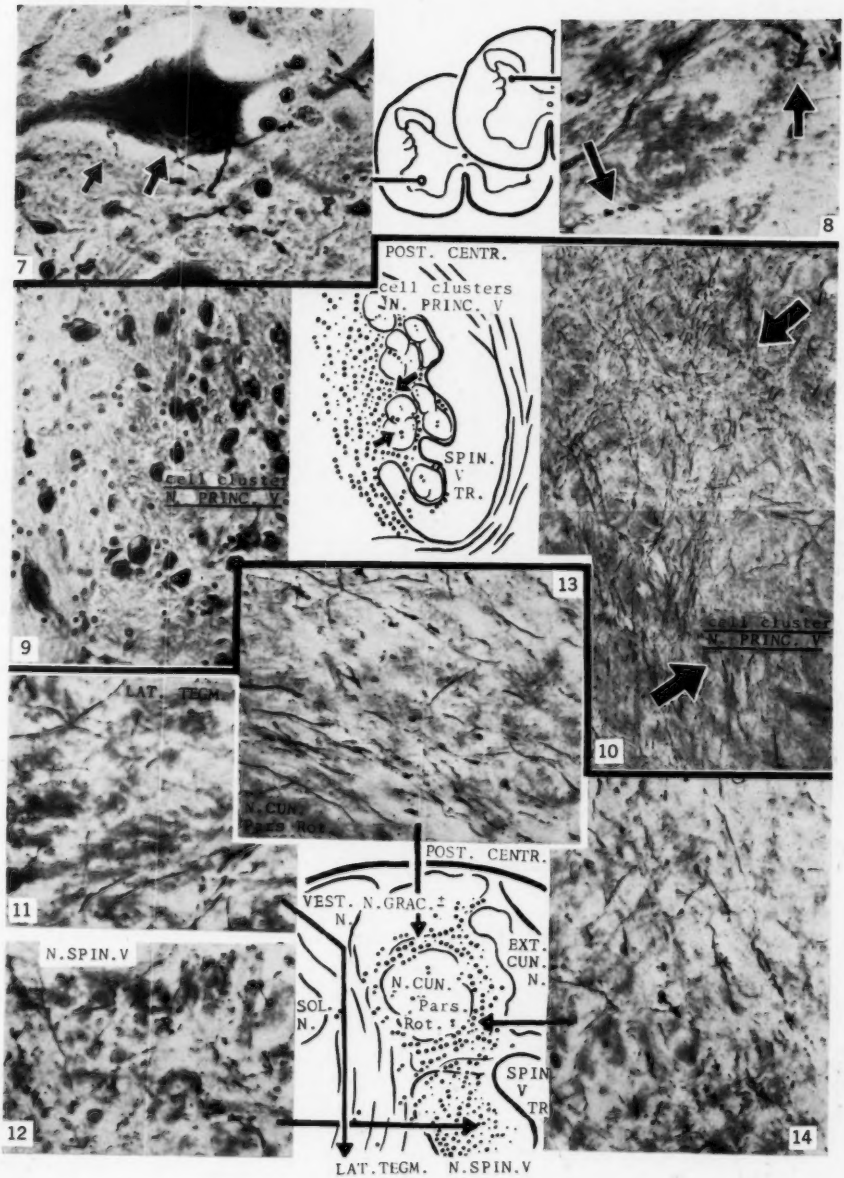
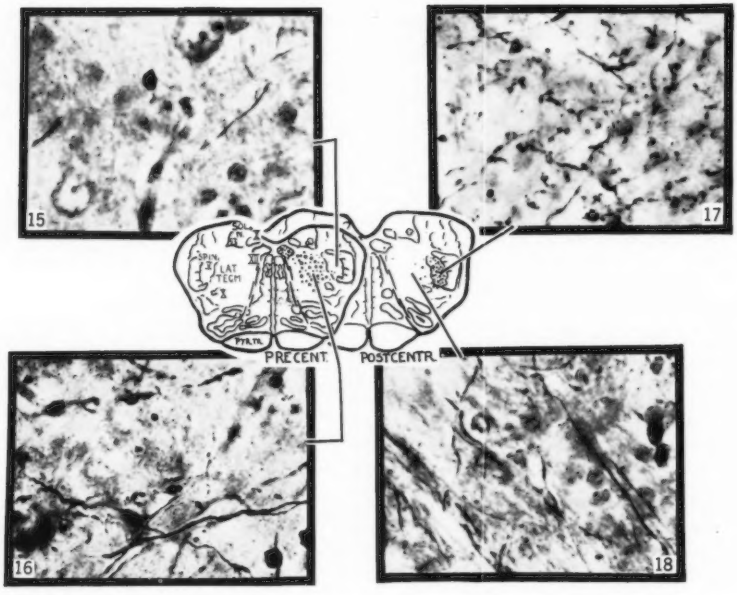
PLATE XXX



To illustrate article by H. G. J. M. Kuypers.

PLATE XXXI



To illustrate article by H. G. J. M. Kuypers.

NOTICES OF RECENT PUBLICATIONS

PÆDIATRIC NEUROLOGY

Pediatric Neurology. By STANLEY S. LAMM, M.D. 1959. Pp. 495. New York: Landsberger Medical Books. Price $12.90.

This book, the work of a man with thirty-five years of pædiatric experience, is a very useful introduction to pædiatric neurology. It is a handy volume which reviews a wide field in relation to its size. Detailed descriptions of neuro-anatomy and of methods of neurological examination are wisely omitted because information of this kind is easy to come by. The book starts appropriately with a brief section on medical genetics and environmental factors which influence growth and development: then follow chapters on mental defect and developmental defects of the nervous system, congenital metabolic defects and congenital disorders due to intra-uterine infections and perinatal calamities which produce the cerebral, spinal, and plexus palsies. Thereafter the book covers most of the neurological disorders of childhood for the most part in a conventional fashion.

It is easy and unjust to criticize a book of this kind for trying to cover too much in too small a space, but where it may be lacking in information it certainly stimulates the reader to get further information elsewhere. Nevertheless, the book is very uneven: thus peroneal muscular atrophy is covered in one page and the fascinating problem of acute infantile hemiplegia in six lines. In contrast such rarities as ataxia telangiectasia receive two pages and Behçet's syndrome one page.

The clinical problem of the limp and floppy baby could have received more detailed consideration, likewise the differential diagnosis of progressive muscular dystrophy. Polymyositis is covered by two short paragraphs and the rôle of dystrophia myotonica in relation to the amyotonia congenita and Möbius syndromes is not mentioned.

The text is easy to read and the general production excellent; but most of the illustrations in the book received were of very poor quality; the air study illustrating agenesis of the corpus callosum, for example, being completely useless. Despite the criticisms made, the book fills a need and will have a wide appeal.

PAUL SANDIFER.

Psychological Appraisal of Children with Cerebral Defects. By EDITH MEYER TAYLOR. Pp. 499. Pub. Commonwealth Fund, Harvard University Press. Price 68s.

All who have had the privilege of knowing the late Bronson Crothers and his team, at the Boston Children's Hospital, working on the problem of the brain-injured child, will welcome this book. Not only is it a comprehensive (here and there even a discursive) study of methods of testing and evaluating the effects of the handicap, but it places its emphasis (as he always did) on the problems facing the brain-injured child as a person.

The arrangement of the book bears this out. A series of clinical studies of individual children, some birth-injured, cerebral-palsied, other children with early

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post-natal damage or with later head injury, are described and watched through successive tests during their early development.

There are many references to test procedures, but not until the clinical picture is vividly presented, and the effect of maturation discussed, are we permitted to read about what tests the author used in order to understand the nature of the handicap, to observe its impact on the learning processes in the child, and to use the results predictively.

No one who attempts this task allotted to the psychologist in such a unit, would ever dream of "giving an I.Q." after a single test. But how often is this done, and asked for by doctors? Decisions may be taken which determine the pattern of educational opportunity for all time, on a single test.

The book is written out of knowledge of just this kind of question which doctors put to their psychologist, and administrators to their school medical officers. Let no one underestimate the value of such apparently simple observations and techniques. They are most lucidly presented; here is an author who really has something of value to describe.

E. M. CREAK.

EPILEPSY

Gli Aspetti Psicopatologici Dell' Epilessia. By E. LUGARESI and M. R. SANDRI. Pp. 302. Edizioni Bologna Medica. No price given.

It is interesting that the emotional background of the occurrence of epilepsy is attracting so much attention in widely separated centres throughout the world, at a time when the neurosurgical attack on the epilepsies is becoming less vigorous. The authors have made a careful neurological and psychiatric study of patients in their clinic who have also been subjected to full electro-encephalographic investigation. The psychological disturbances they discuss range from the immediate effects of the attacks through the neuroses associated with epilepsy, and the behaviour disorders associated with cerebral damage, to the criminal aberrations of some epileptic subjects. The authors make full use of their knowledge of English-speaking and French literature, which is contained in chapter bibliographies.

DENIS WILLIAMS.

NEUROCHEMISTRY

Heavy Metals and the Brain. By J. N. CUMINGS. Pp. 155. Oxford: Blackwell's Scientific Publications. Price 32s. 6d.

It must be said at once that this monograph deals with copper, mercury and lead, approximately half the volume being devoted to copper with special reference to hepatolenticular degeneration. The field, therefore, is limited, but within these limits this is an absolutely first-class review of available information, welding clinical and laboratory data with remarkable lucidity and singular freedom from bias.

It is very fully documented and carries the hallmark of the work of a widely educated writer who has a profound knowledge of the subject. The reviewer's one regret is that the author, scrupulously fair to the many contributors to the field, nowhere allows himself space for speculation on the problems that this factual review discloses. Such speculation may have been outside his terms of reference.

With deference in such an excellent production a minuscular criticism must be made of errors in numbering of the comprehensive list of references at the end of the monograph.

NICHOLAS MARTIN.

TRIGEMINAL NEURALGIA

Trigeminal Neuralgia: Its History and Treatment. By BYRON STOOKEY, A.M., M.D., and JOSEPH RANSOHOFF, M.D. 1959. Pp. xv+366. Oxford: Blackwell Scientific Publications. Price £4 1s.

"*Classic*, any great writer or work: a standard work. *Classical*, of the highest class or rank, esp. in literature."—*Chambers's Dictionary*.

What would be the marks of "an eminently classical monograph" by a surgeon on a single disease?

On its dust-cover it would probably not describe itself in those words, nor its author's 656 analysed cases as "over 700." Its choice of a name for the disease would not fall on one which, being applicable to other disorders, fostered harmful contradictions ("There were nine patients with atypical trigeminal neuralgia whose pain was sufficiently characteristic and severe to warrant posterior root section"). It would not say "*Definition:* Apparently some confusion has existed as to exactly what constitutes trigeminal neuralgia," and then offer no definition.

It would avoid suggesting that Aretaeus wrote a book called *The Cappadocian*, or Avicenna one called *The Cannon of Medicine*. Its reviewer would be spared the task of pointing out such facts as these: that Fehr & Schmidt first published their eulogy of Bausch in 1671 (not 1688), that "the toxic effects of trichlorethylene" noted in 1943 were shown in 1944 to be effects of dichloro-acetylene, that an article which the author attributes to Adams-and Robinson is really by Cooper and vice versa, that Kulenkampff in the paper cited did not "report on the use of X-rays," that Zenker in 1938 recorded not "4 deaths in 500 cases" but 5 in 325, that Tiffany made his first suggestion for partial gangliectomy in 1894 (not 1896); that Augusta Taurinorum, accidentally, Colman (Horsley's collaborator), curiosorum, engorgement, ferrous, Kanavel, Kulenkampff, van Nouhys, trismus dolorificus and vertical are so spelt; that titles of works in foreign languages, if quoted in full, should be quoted correctly; that "precipitously" differs from precipitately, "masterful" from masterly, "tearing" from lachrymation and the *Lancet* from the *Lancet-Clinic* of Cincinnati.

On subjects of slight or purely potential relevance it would touch briefly if at all. In the case of tic douloureux it would probably not devote 20 out of 307 pages of text to embryology and comparative anatomy, nor 32 to physiology including 17 on the taste pathway.

In expounding positive diagnosis, especially of a disabling, widely misdiagnosed and curable disease, it would be a model of thoroughness, clarity, good arrangement and proper emphasis. It would not state that the diagnosis rests exclusively on the history and the character of the pain, and yet that the patient's behaviour and appearance are diagnostic aids. It would deal with the spatial and temporal distributions of pain consecutively and not in alternating fragments. It would not stress an inconstant and non-specific feature ("The pain seldom occurs at night") while leaving the most specific of all, namely the precipitating factors, to be inferred from three scattered remarks, supplemented by a reference to certain seventeenth- and eighteenth-century writers. Differential diagnoses, on the other hand, it would summarize in fewer than 27 pages, without historical or therapeutic digressions.

It would rise above the current bias of the author's nation and speciality. If it spent 45 pages on historical and other aspects of subtemporal rhizotomy, 23 on suboccipital rhizotomy, 28 on tractotomy, 11 on other forms of surgery and 10 on peripheral injection, it would assuredly allot more than 3 to all aspects of sensory-root or "ganglion" injection ("still not commonly done" in the United States).

It would supply all cardinal references: for example, Mayo as well as Bell on the functions of the fifth and seventh cranial nerves, since, as Fulton has remarked, Bell just missed the discovery and Mayo deserves the credit; Sicard and Ferner for

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anatomy of the trigeminal motor and sensory roots; Palthe and Kugelberg for trigeminal reflexes; Bjerrum and Thornval for a recent ætiological theory (or was it too recent?); Parker for an acoustic neuroma and Hamby for a contralateral posterior-fossa meningioma, each associated with true tic douloureux; Taptas for the first sensory-root injection; Härtel and several later workers for this type of injection under radiological control. Inessential references, on the other hand, it would omit: what if in 1804 John Fothergill's verbose nephew did "add little to what was already known," or if by 1918 one Camp had renounced "ganglion" injection because there was "only a question of time until I should kill somebody"?

Its crown would be the author's own operative statistics, for whereas others might have written the rest, here we should have the unique product of his hands. He would have instituted a follow-up by interview when he began his series of operations, and the records of 14 patients would not be mislaid. Nor would death mean that "adequate follow-up was not possible," but the very opposite: what could be more adequate than follow-up to the grave? Thus he would have lost touch with fewer than 46 per cent of his patients, and would not be compelled to present those "permanently relieved" as 87 per cent of the remaining 54 per cent. Nor would he be content to define permanent relief as "freedom from pain for at least eighteen months," but would require satisfactory objective findings on clinical examination at several interviews. Long-term results could then have filled a solid chapter instead of two disappointing pages.

Though not a classic, this book has good points, of which the chief are a judicious assessment of the rival major trigeminal operations, and an almost wholly excellent chapter on the historical background of sensory-root section. A pity that the claims made for it, and the price asked, are not more moderate.

JOHN PENMAN.

HEAD INJURY

Head Injuries. By E. S. GURDJIAN, M.D., and J. E. WEBSTER, M.D. 1958. Pp. 482. London: J. & A. Churchill. Price £5.

Chronic Subdural Hematoma. By RAGNAR NORDLIE. 1958. Pp. 163. Oslo: Johan Grundt Tanum Forlag. Price £5.

The American book is a comprehensive account of the practical aspects of head injuries. The authors state:

"This volume reflects our experience—clinical, neurosurgical and experimental, civilian and military—with head injuries. In its preparation, material collected for twenty-five years has been reviewed, including data derived from 1,285 cases of head injury treated at the Detroit Receiving Hospital between January 1952 and July 1954; from 151 consecutively autopsied cases of head injury; and from a large collection of experimental material, mainly on the mechanics of head injury." They have succeeded admirably in presenting the clinical and neurosurgical sides of the subject and their own experimental work, particularly in relation to the production of fractures and the mechanics of head injuries, although the application of this to neurological disturbance is less successful.

Surely the authors hold the mid-brain reticular formation to be responsible for more than the present evidence justifies. The more modern views on the management of the severe head injury by means of tracheotomy, temperature control and its related drugs are mentioned, but apart from the undoubted value of tracheotomy, not surprisingly no conclusive statements are made about the value of the other measures. The chapters on post-traumatic psychiatric states and on medico-legal considerations do not rise above the ordinary level.

This is a useful book for both neurological and general surgeons. The references with each chapter are admirable and the production leaves little to be desired. Both

Drs. Gurdjian and Webster and Dr. Nordlie in his detailed monograph on Chronic Subdural Hæmatoma are convinced of the value of ancillary methods of diagnosis of space occupying clots which complicate head injuries. Carotid angiography was almost always used in the latter's series of 50 subdural hæmatoma, reflecting the growing feeling that when there is time to spare, the more accurate localization achieved by angiography is preferable to numerous exploratory burr holes.

The monograph on "Chronic Subdural Hæmatoma" gives a detailed account of the history of this condition with particular reference to the views of Virchow (Pachymeningitis hæmorrhagica interna) and Trotter's accurate and illuminating paper on the condition in 1914. The author describes the varying clinical manifestations and gives a most exhaustive account of the value of angiography, pneumencephalography and electroencephalography. One gathers that this diagnostic barrage would rarely be considered necessary, but it is interesting to compare the different methods applied to a series of cases such as this. Dr. Nordlie is particularly concerned with diagnosis. His views on treatment are a little rigid. The patient's age may determine the operative method, as he expects to find organized hæmatomas below the age of 50 and liquid hæmatomas over that age. "Those around 50 may be considered an intermediate group in whom both fluid and organized hæmatomas occur." Burr holes are, therefore, used below the age of 50 and craniotomy above that age. Although these observations are in general true they hardly justify such a rigid surgical programme.

JOHN HANKINSON.

NEUROANATOMY

The Postnatal Development of the Human Cerebral Cortex. Volume VI: The Cortex of the Twenty-four-month Infant. By J. LeRoy Conel. Harvard University Press. London: Oxford University Press. Price £5.

Professor LeRoy Conel must be congratulated on this sixth volume of his admirable series on the postnatal development of the human cerebral cortex. In previous volumes the brains of infants at birth, and at 1, 3, 6 and 15 months after birth have been described. The present volume follows the same pattern as its predecessors. An essential part of the book is the large number of photographs and drawings from Golgi-Cox preparations of the cortex. The high standard of the sections is particularly impressive in view of the increased age of the brains forming the basis of the present study.

Using the same nine criteria as before, it was found that, as would be expected, there is an advance in the development of the cortex throughout the hemispheres. In certain regions the advance is more marked than in neighbouring regions. One of the objects of the investigation was a correlation between the development of the cortex and the development of behaviour in the human. An important example of this aspect of the study is the observation that in the frontal cortex the advance in development is more marked in FAγ than elsewhere. Within this area the regions of trunk, shoulder, arm, forearm and hand are more advanced than the region of head, which is more advanced than that of the lower extremity. It was noted that the cortex of the middle frontal gyrus, which lies immediately anterior to the motor region associated with the hand in the cortex of the 24-month infant, is more advanced than the cortex in the superior frontal gyrus, which lies anterior to the region of the lower extremity, or in the inferior frontal gyrus, which is anterior to the region of the head and includes Broca's area of speech. The advance in development in the cortex in the three frontal gyri suggests that the cortex of these gyri may be exerting control over the region of the primary motor area FAγ.

Some slight suggestion of handedness in the cortex is present at this stage, a difference in degree of development between the right and left hemispheres in the region of the hand being noticeable in some of the brains.

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In keeping with the development being most advanced in the motor area of the frontal lobe, it is also most advanced in the primary somesthetic centre, the gyrus centralis posterior in the parietal lobe in the primary afferent centre for vision, OA, in the occipital lobe, and the primary afferent centre for sound, TC, in the temporal lobe.

Another feature of the study is a discussion of the character and possible relationships of various groups of nerve fibres in the cortex. It is stressed how little is known about intra-cortical connexions in the human. The author therefore passes into a theoretical discussion of neuronal functioning which might explain the development of certain fibre patterns. He finds that, according to Kappers' theory of neurobiotaxis, that "electric potentials produced in the central nervous system itself play the most important role in determining the outgrowth of neurons," the dendrites of neurones grow towards the source of stimulus and the axon away from it. If the neuron itself is regarded as the source of the action current, then the growth of the axon of a cell in the cerebral cortex is regarded as being in accordance with the theory of neurobiotaxis. The phylogeny and ontogeny of the nerve cell are considered at some length, largely in relation to the cerebrospinal fluid and the hypothesis that the action current is generated in the neuron itself is proposed.

This theoretical discussion is the final part of the book. Although interesting, it invokes some regret that a work of such magnitude in relation to facts does not end on a factual note.

One other minor criticism is that in this section of the book, called Comments, there is little or no summing up of each point discussed before a new point is introduced.

These are, however, very small criticisms of a work of outstanding value.

MARION C. SMITH.

NEUROPHYSIOLOGY

Handbook of Physiology. A Critical Comprehensive Presentation of Physiological Knowledge and Concepts. Section 1 *Neurophysiology*, Editor in chief JOHN FIELDS, Section Editor H. W. MAGOUN, Executive Editor VICTOR E. HAWE, American Physiological Society, Washington, D.C. Volume 1, 1959. Pp. 779, price $22 or 176s. Volume 2, 1960. Pp. 659, price $20 or 160s. Distributed by Williams and Wilkins, Baltimore, and Baillière, Tindall and Cox Ltd., London.

It is difficult to praise these magnificent volumes too highly. As the general preface states the handbook "is designed to constitute a repository for the body of present physiological knowledge, systematically organized and presented. It is addressed primarily to professional physiologists and advanced students in physiology and related fields. Its purpose is to enable such readers, by perusal of any section, to obtain a working grasp of the concepts of that field and of their experimental background sufficient for initial planning of research projects or preparation for teaching. To accomplish this purpose the editors have planned a book which would differ from textbooks in being more complete, more analytical and more authoritative." A random selection of the subjects and authors of some chapters will give the potential reader a good idea of the scope of these two volumes and the standard aimed at by the editors. J. C. Eccles writes on neuron physiology; Von Euler on autonomic neuro-effector transmission; Lord Adrian on sensory mechanisms; Ragnar Granit on neural activity in the retina; Derek Denny-Brown on motor mechanisms: the general principles of motor integration; David P. C. Lloyd on spinal mechanisms involving somatic activities; C. W. Harris on central control of pituitary secretion; D. Whitteridge on central control of eye movements; F. Bremer on central regulatory mechanisms; J. D. French on the reticular formation, and Herbert H. Jasper on unspecific thalamocortical relations.

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The achievement matches the aim. In these two volumes there are 58 chapters, each authoritative, well arranged, well illustrated and well documented with references. The editors are to be congratulated on a major contribution to medical literature which will be indispensable to all who wish to have access to the great accumulation of recent new knowledge in the rapidly expanding field of neurophysiology.

W. RUSSELL BRAIN.

NEURORADIOLOGY

Cerebral Angiography in the Management of Head Trauma. By CHARLES A. CARTON, M.D., Professor of Neurosurgery, Veterans Administration Hospital, Houston, Texas. 1959. Pp. 157. Oxford: Blackwell. Price 52s. 6d.

This small monograph presents a review of the literature on cerebral angiography in cases of head injury, and an analysis of 103 cases examined by this method in three different hospitals in Houston, Texas.

The examinations were carried out and interpreted by many different neurosurgeons and radiologists, and were assembled for review by the author, who confirms the value of the procedure. There are 44 illustrations, but many of the angiogram reproductions are of poor quality.

Intracranial Calcification.—By F. MASCHERPA and V. VALENTINO. Milan Neurological Institute. Vincenzo Valentino Radiologist, Naples University. 1959. Pp. 150. Oxford: Blackwell. Price 72s.

This volume is in effect a descriptive atlas of normal and abnormal intracranial calcification. It is profusely illustrated and the illustrations are of generally high quality. It is based on a study of 153 cases collected from the material of the Milan Neurological Institute, and it is claimed in the introduction that 70 per cent of these cases were surgically or pathologically verified, though no surgical or pathological evidence is given in the text. The reviewer would have preferred to see some of the pathological evidence detailed and presented, particularly in the case of controversial lesions such as "calcified gumma" and "calcified tuberculoma."

Generally speaking, however, this is a comprehensive and useful atlas, and can be recommended to both neurologists and radiologists.

DAVID SUTTON.

SHORTER NOTICES

Die Cerebrale Gefäss-sklerose. By Dr. HANS E. KEHRER. Diagnose, Behandlung und Soziale Aspekte. 1959. Pp. 238. Stuttgart: Georg Thieme Verlag. DM 28.00.

Das Hirngeschädigte Kind. Psychologie und Diagnostik. Eine Experimentalle Untersuchung. By Prof. KARL-HERMANN WEWETZER. 1959. Pp. 117. Stuttgart: George Thieme Verlag. DM 19.80.

Readings in Psychoanalytic Psychology. Ed. MORTON LEVITT, Ph.D. 1959. Pp. 413. London: Staples Press. Price 70s.

Twenty-four American analytical psychiatrists and a professor of English have combined to produce a book which "in a modest way attempts to provide in one place reliable source material for students of the behavioural sciences." As inclusively as possible they have reviewed the basis of psychoanalytical theory and therapy.

The Effect of Pharmacological Agents on the Nervous System. Res. Publ. Ass. Nerv. ment. Dis. Vol. 37. 1957. Pp. 488. London: Baillière, Tindall and Cox. Price 108s.

The form and content of this volume, which contains the proceedings of the meetings held in New York two years ago, follow the pattern of its predecessors. There are 26 essays on pharmacology and the nervous system, including a salutary one on placebos, which may surprise the clinician, summed up in the sentence, "It is

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important to realize that placebo effects are not imaginary," for many of the effects are unexpected and profound.

Operative Surgery. Eyes, Ear, Nose and Throat. Neurosurgery. 1959. Pp. 196. London: Butterworth. Price £9.

Those parts of each of the eight volumes of the illustrated surgery edited by Professor Charles Rob and Mr. Rodney Smith which related to the nervous system and special sense organs have been collected into an independent volume. Mr. Wylie McKissock edits the neurosurgery and Sir Stewart Duke-Elder the Ophthalmology.

Travaux Scientifiques. By J. NICOLESCO. 1959. Pp. 616. Paris: Masson et Cie.

His colleagues in Bucharest, led by Dr. Nicolau have compiled a memorial volume to Professor Jean Nicolesco. Though Rumanian, Professor Nicolesco was much influenced by French neurology, and it is both fitting and fortunate for us that this volume, produced in Rumania, is all in French. It is not simply a collection of his 200 papers on neurological anatomy and pathology. The more important of the original papers are grouped according to subjects and reproduced in full or in summary. The volume is well organized into fourteen chapters which range through neurology. It is magnificently produced and illustrated, and is a valuable work of reference as well as a personal monument.

Strong and Elwyn's Human Neuroanatomy. By RAYMOND C. TRUEX, Professor of Anatomy, Hahnemann Medical College. Fourth Ed. 1959. Pp. 511. London: Baillière, Tindall and Cox. Price 80s.

This text for senior students has reached four editions since 1943. It relates the generally accepted pattern of morphology of the nervous system to its physiological background. The general format is that of other standard neuroanatomical texts, which it also resembles closely in its illustrations and page structure. Its bibliography is representative and up to date.

International Review of Neurobiology. Ed. CARL C. PFEIFFER and JOHN R. SMYTHIES. Pp. 383. London: Academic Press. Price $10.

In this first volume there are eight sections, by authors from several countries, viz.: Recent Studies of the Rhinencephalon in Relation to Temporal Lobe Epilepsy and Behaviour Disorders, by W. R. Adey; Nature of Electrocortical Potentials and Synaptic Organizations in Cerebral and Cerebellar Cortex, by Dominick P. Purpura; Chemical Agents of the Nervous System, by Catherine O. Hebb; Parasympathetic Neurohumors; Possible Precursors and Effect on Behaviour, by Carl C. Pfeiffer; Psychophysiology of Vision, by G. W. Granger; Physiological and Biochemical Studies in Schizophrenia with Particular Emphasis on Mind-Brain Relationships, by Robert G. Heath; Studies on the Role of Ceruloplasmin in Schizophrenia, by S. Martens *et al.*; Investigations in Protein Metabolism in Nervous and Mental Diseases with Special Reference to the Metabolism of Amines, by F. Georgi *et al.*

Each is an invaluable review of present knowledge, fully documented for the specialist in that field. Presumably the biochemical essays, which are beyond the reviewer's competence, have the same high standard as those dealing with the rhinencephalon and with electrocortical potentials, which are quite outstanding.

Recent Neurological Research. By A. BIEMOND *et al.* Professor of Neurology, University of Amsterdam. 1959. Pp. 330. London: Elsevier. Price 47s. 6d.

The Amsterdam Neurological Society recently celebrated its fiftieth anniversary in a meeting to which foreign guests were invited. The Agenda consisted of papers by these guests but in return the hosts presented a volume of twenty-eight monographs by their members. These range throughout neurological medicine, surgery, histology and related subjects to give a vivid impression of the enquiring attitude which has always characterized Dutch neurology. The book can be used as a pleasant

series of essays rather than as a work of reference. It will be welcomed by the many authors' friends throughout the world.

First International Congress of Neurological Sciences. Brussels July 21–28, 1957. Vol. III. Pp. 704. London: Pergamon Press. Price £7.

This volume which contains papers given at the combined meeting with the Fourth International Congress of Electroencephalographs and Clinical Neurophysiology, and the Eighth Meeting of the International League Against Epilepsy seems the ultimate condemnation of giant congresses. The editors have done their best, but the large volume contains a tedium of abstracts in several languages. Facts are buried in an expensive mass grave, their epitaphs the one minute index which occupies less than three of the 700 pages. Fortunately it is the custom to publish elsewhere also, for there are some distinguished authors and good papers.

Electromyographie dans les Maladies Nerveuses et dans la Cryptotetanie. By N. ROSSELLE (with the Collaboration of K. DE DONCKER, P. JOLIE and S. LIGOT). 1959. Pp. 159. Paris: Nauwelaerts. Price 46s. 6d.

In his preface the author states that this book is intended for those who wish to familiarize themselves with the subject of clinical electromyography without requiring a detailed account of its theoretical background or its technical detail. Accordingly, basic physiology and recording technique are each dismissed in a single paragraph and the electrical behaviour of normal muscle and its nerve supply receives only three pages of text and some illustrative records. This is followed by the systematic presentation of pathological conditions; in this section there are fifty-five illustrations of specimen records with sixteen pages of text.

The remainder of the book (ninety pages) is described as an atlas of electromyography and is devoted to the reproduction of records from individual clinical cases, with only a few lines of explanatory lettering in each case. Owing to the absence of adequate clinical information, this section has little interest for those already working in the field, and as a method of teaching it is open to the criticism that it encourages the student to associate certain electromyographic patterns with particular clinical diagnoses without any appreciation of the underlying physiology.

The Historical Development of Physiological Thought. A Symposium Held at the State University of New York, Down-State Medical Center. Edited by CHANDLER MCC. BROOKS, and PAUL C. CRANEFIELD. 1959. Pp. 401. New York: de Hafner Publishing Company. Price 45s.

The Central Nervous System and Behaviour. Transactions of the First Conference. Edited by MARY A. B. BRAZIER, Ph.D. Sponsored by the Josiah Macy, Jr., Foundation and the National Science Foundation, New York. 1959. Pp. 450. Price $5.25.

Both of these books are historical. The Historical Development of Physiological Thought devotes a good deal of space to neurology with chapters on the development of ideas on the synapse by Sir John Eccles, historical reflections on the background of neurophysiology by Professor Fulton, development of ideas relating the mind with the brain by Dr. Magoun and the biology of consciousness by Dr. Homer Smith. There are also chapters on the history of the discovery of the chemical transmitters and the development of endocrinology.

The Central Nervous System and Behaviour is a historical review of the Russian contribution to neurophysiology with particular reference to Pavlov and his followers. Dr. Horsley Gantt writes on Pavlov, Professor Yakovlev on Bechterev, and Drs. Howard Liddell, Olds and Sperry on post-Pavlovian development in conditioned reflexes. There are also up-to-date studies of brain stimulation in conditioned reflexes and the electrophysiological aspects of conditioned learning.

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The Anastomoses Between the Leptomeningeal Arteries of the Brain. Their Morphological, Pathological and Clinical Significance. By HENRI M. VANDER EECKEN, M.D., Professor of Medical Psychology and Agrégé in Neurology, Faculty of Medicine, the University of Ghent, Belgium. Preface by Raymond D. Adams. Charles C Thomas, Springfield, Ilinois, U.S.A., and Blackwell Scientific Publications, Limited, Oxford. 1959. Pp. 160. Price 57s. 6d.

This little book is of particular interest at a time when the cerebral circulation and its disorders are attracting so much attention. The author reviews the arterial blood supply of the brain with particular reference to the anastomoses provided by the leptomeningeal arteries. He discusses the functional significance of these, particularly in the cortical border areas of the distribution of the main arteries in cases of softening of the brain, and he reaches the conclusion that these anastomotic vessels may be a factor in limiting the extent of softening in the cortico-subcortical region of both the cerebrum and the cerebellum.

Speech and the Development of Mental Processes in the Child. An Experimental Investigation by A. R. LURIA and F. I. YUDOVICH. Edited by Joan Simon with an introduction by Professor Oliver Zangwill. 1959. Pp. 126. London: Staples Press. Price 15s.

This is a study of the development of speech in a pair of uniovular twins. The twins initially exhibited retarded primitive speech. They were separated and placed in separate parallel groups in a kindergarten and the changes which took place in their speech were observed. Subsequently a special systematic experiment in teaching speech to one of the twins was carried out. The book reports first the effect of breaking up the twin situation and then of the special training of one twin, the other being left as a control. The development of speech was shown to call for significant changes in the structure of thought and consciousness.

Biological and Biochemical Bases of Behaviour. Edited by HARRY F. HARLOW and CLINTON N. WOOLSEY. 1958. Pp. 476. Madison: University of Wisconsin Press. Price $8.

This volume contains the contributions to yet another symposium on interdisciplinary research. Most of the articles are reviews of recent work on some aspect of the neurophysiology of behaviour. Dr. Magoun writes on non-specific brain mechanisms and Dr. Jasper on reticular-cortical systems and theories of the integrative action of the brain. Dr. Woolsey deals with the organization of somatic sensory and motor areas of the cortex and, in association with Dr. Rose, on the thalamic auditory system of the cat. Dr. Pribram discusses neocortical function in behaviour. The neurochemical aspects of behaviour also receive consideration and Dr. Hebb winds up with a paper entitled "Alice in Wonderland or Psychology among the Biological Sciences."

ANNOUNCEMENT

The next International Congress of Neuroradiology (VI Symposium Neuroradiologicum) will be held in Rome from September 18–22, 1961, under the Presidency of Dr. Giovanni Ruggiero. All correspondence should be addressed to Dr. Enzo Valentino, General Secretary, VI Symposium Neuroradiologicum—CIT—Ufficio Congressi Piazza Colonna 193 Rome.